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DETERMINANT FACTORS OF RESPONSE TO ANTIRETROVIRAL TREATMENT AMONG HIV/AIDS PATIENTS IN BELLA DEFENCE HOSPITAL

A THESIS SUBMMITED TO THE SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF GONDAR, IN PARTIAL FULLFILMENT OF THE REQUIRMENTS FOR THE DEGREE OF MASTER'S IN PUBLIC HEALTH

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LIST OF ABBREVIATIONS

AIDS	-	Acquired Immune Deficiency Syndrome
ART	-	Antiretroviral Therapy
ARV	-	Antiretroviral
ABC	-	Abacavir
AFB	-	Acid fast bacilli
AZT/ZDV	-	Zidovudine
AZT	-	Zidovudine
ACM	-	Advanced Clinical monitoring
AFTGH	-	Armed Forces Teaching General Hospital
CDC	-	Centre for Disease Prevention and Control
CBC	-	Complete Blood Count
CD4	-	Cells with CD4 marker
DHD	-	Defence Health Department
DNA	-	Deoxyribonucleic acid
DOTS	-	Directly Observed Therapy Short Course
DDI/ddI	-	Didanosin
d4T	-	Stavudine
EFV	-	Efavirenz, also abbreviated as EFZ
ELISA	-	Enzyme Linked Immunosorbent Assay
FHAPCO	-	Federal HIV /AIDS Prevention and Control Office
FDA	-	Federal drug administration
FBS	-	Fasting Blood Sugar
GOE	-	Government of Ethiopia
HAART	-	Highly Active Antiretroviral Therapy
HCT-HIV	-	Counselling and Testing
HIV	-	Human Immunodeficiency Virus
HIVDR	-	HIV Drug Resistance
HAPCO	-	HIV/AIDS Prevention and Control Office
HBV	-	Hepatitis B virus
HCV	-	Hepatitis C virus
IDV	-	Indinavir
IRB	-	Institutional Review Board
LFT	-	Liver Function Test
LPV	-	Lopinavir
MOH	-	Ministry of Health
MD	-	Medical Doctor
µl	-	micro-litre
ml	-	millilitre
MTCT	-	Mother-To-Child Transmission (of HIV)
NFV	-	Nelfinavir
NNRTI	-	Non-nucleoside reverse transcriptase inhibitor
NRTI	-	Nucleoside Reverse Transcriptase Inhibitor
NVP	-	Nevirapine
OIs	-	Opportunistic Infections
OI	-	Opportunistic Infection

PCP	-	Pneumocystis pneumonia
PCR	-	Polymerase chain reaction
PEP	-	Post-exposure prophylaxis
PI	-	Protease Inhibitor
PLWHA	-	People living with HIV/AIDS
PMTCT	-	Prevention of mother-to-child transmission (of HIV)
PHE	-	Public Health Evaluation
PI	-	Principal Investigator
PI/r	-	Ritonavir boosted Protease Inhibitor
RNA	-	Ribonucleic Acid
RT	-	Reverse Transcriptase
RNA	-	Ribonucleic acid
RTV, r	-	Ritonavir
RFT	-	Renal function test
SPSS	-	Statistical Package for the Social Sciences
SQV	-	Saquinavir
STD/STI	-	Sexually Transmitted Disease/Sexually Transmitted Infection
TDF	-	Tenofovir
3TC	-	Lamivudine
TLC	-	Total Lymphocyte Count
UCSD	-	University of California, San Diego
UNAIDS	-	Joint United Nations Programme on HIV/AIDS
WHO	-	World Health Organization
ZDV	-	Zidovudine (also abbreviated as AZT)

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ABSTRACT

Background: The Ethiopian ART program has improved survival of patients thru increasing access to ART. Many patients fail to benefit from ART because of early drug intolerance, poor adherence, and potentially other reasons. Causes of variation in reported treatment outcomes from the ART programs in developing countries such as Ethiopia is unclear. Identification of the determinants of the ART outcomes could support evidence-based improvements in ART in Ethiopia and other resource limited settings (RLS).

Objective: To investigate the pattern of immunologic and clinical responses and the risk factors for poor outcomes from ART

Methods: This retrospective cohort study of adult patients who were started on ART between 06/97 to 5/01 (Ethiopian Calendar) describes correlates of survival and other measures of response to ART. Data was retrieved from the national ART recording formats in Bella Defense Hospital, a major Ethiopian Military Hospital which provides free HIV care to a diverse population of soldiers, their dependents and retired members. Data were collected by clerks and nurses as part of routine clinical documentation. Kaplan Meier analysis estimated the survival time probability following initiation of ART and log-rank test measured the significance of differences in survival times. Cox proportional hazards models used to determine the hazard of the outcome variables for the levels of the determinant factors of the outcome.

Results: Mean follow up time was 12.5 months and median was 8 months. Most commonly used ART regimens were D4T, 3TC, and NVP (45%) and AZT, 3TC, NVP (31%). Of the 709 patients, 18% died and 9.3% were lost to follow up, 25% transferred out and 47% remained in follow-up. Of the 16% who had changed their first regimen, 64% did so for side effects, 23% for new TB and 6% for treatment failure. During the follow up there were 61(8.6%) new TB, 8(1.1%) new OIs, and 75(10.6%) recorded major side effects. The mean failure free survival time estimated for the whole cohort by Kaplan Meier analysis was 29.months. Almost 2/3 of response failures (64%) occurred during the first three months after starting ART. Many factors (age >50, male sex, base line CD4 cell count <100, low weight, advanced WHO stages, and TB treatment at the start of ART) were found to be predictors of failure in bivariate Cox proportional hazard model. In a multivariate model, only poor/fair adherence was predictive (HR=5, $p < 0.001$), pre-treatment exposure to ARV (HR=4.2, p=0.002), side effects of ART (HR=2.1, p=0.002), and low functional status [bedridden] (HR=2.1, p=0.004) remained statistically significant ($p < 0.05$). Hemoglobin <10mg/dl (HR=1.7, p=0.04) was also an important factor when functional status was removed from the model. Poor /fair adherence decreased survival by 14 to 20 months than good adherence in the cohort.

Conclusion and recommendations: As have other studies in RSL, this one found that failure of ART, including death, was associated with prior ART exposure, indicators of advanced HIV clinical stage, co-infection with TB, and poor adherence. The majority of deaths occurred within three months of starting ART, but reasons for this early mortality are unclear. Investigating reasons for early deaths, the role of drug resistance as a mechanism of ART failure, and strategies to enhance adherence are promising strategies for reducing ART failure.

DECLERATION

I, the undersigned declare that this thesis is my original work in partial fulfillment of the requirement for the degree of Master of Public Health. I also declare that it has never been presented in this or any other university and that all resources and materials used in the thesis have been duly acknowledged.

Student Name:___Samuel H/Mariam,MD

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Place of submission: _____

Date of submission: _____

This thesis has been submitted for examination with my approval as a university advisor.

Advisor Name: _____

Signature: _____ _____ _____ _____

Date of submission: _____

I. Introduction/Background Information

With the advent of ARV drugs, AIDS has become a treatable chronic disease. Even in a Third World setting with increasing people with AIDS accessing services, a decline in death rates is clearly visible. In resource-limited settings patients accessing ART have a number of non-medical needs including nutrition, shelter, transportation etc. A social system addressing these supports drug adherence. The public health approach, recommended by WHO for resource-poor settings, is an overarching principle of the Ethiopian ART program. By this approach, large numbers of people are facilitated to access ART and survival is maximized (1). Even though there are good responses for the ART, reasons for the variation in reported treatment outcomes from the ART programmes in developing countries, are not clearly defined (2).

Based on various facts the time to initiate varies from one country to others and it is believed that the time of initiation affects the response or outcome to ART. The scientific indication for antiretroviral therapy is based on the clinical assessment, CD4+ T-cell count, and viral load. At first glance, it appears straightforward: the lower the CD4+ T-cell count and the higher the viral load, the higher the risk of AIDS (42, 43), and the more urgent the indication for treatment. Nevertheless, the best time for initiation of therapy remains the subject of controversial debate. The risk of AIDS must be weighed against the risks of long-term toxicity and viral resistance. These risks and the realization that eradication cannot be achieved at present have led to less rigid guidelines in many countries in recent years.

The question now is how to practically apply the new, more appealing motto of, hit hard but only when necessary (44). At least all international guidelines agree that all symptomatic patients as well as patients with less than 200 CD4+ T-cells/µl should be treated. However, for patients with more than 200 CD4+ T-cells/µl, the situation becomes more confusing. Lack of

randomized studies forces all guidelines to rely on cohort studies, meta-analyses and evaluation of larger databases.

ART in Ethiopia

Ethiopian guidelines for Antiretroviral Therapy in adults and adolescents (1,40): the guidelines standardize and simplify the initiation and monitoring of ART; Standardized formulary for first and second-line ART, with the use of two NRTIs and an NNRTI as the standard first-line approach, reserving PIs for second-line is the center piece of the public health approach to ART. The Ethiopian National Defense Forces HIV/AIDS program also follows the national guidelines.

A. When to start

Table.1: Criteria for initiation of ART in adults and adolescents in Ethiopia, FHAPCO, 2007

CD4 count not available	CD4 count available
WHO clinical stage IV and III irrespective of Total Lymphocyte Count (TLC)	WHO clinical stage IV, irrespective of CD4 count
WHO Clinical stage II if TLC <1200/ mm3	WHO clinical stage III, if CD4 cell counts ≤350/mm3
Do not treat WHO clinical stage I, in absence of CD4 count	All WHO clinical stages, if CD4 cell counts <200/ mm3
TLC is only useful in deciding when to initiate ART in symptomatic patients with WHO clinical stage II disease. The use of CD4 cell count to guide treatment decision is advisable. For example, pulmonary TB may occur at any CD4 level and other conditions may be mimicked by non - HIV etiologies.	

The Ethiopian defense forces ART facilities also follow the national treatment guideline.

B. ARV regimens

First-line ARV regimens for adults and adolescents

The preferred first-line regimen consists of NRTI backbone with one of the NNRTIs. Both NNRTIs are given equal preference; choice is based on patients' conditions. ABC and TDF are included in this guideline to expand the choice and tailor to specific patient needs. ABC is used in triple NRTI regimen in rare patients with TB and pregnancy, or other situations when the

standard first-line regimens may not be given. Both ABC and TDF are reserved for the second-line regimen. (ABC and TDF are only available recently since 2008).

One of the following should be used unless there are contraindications:

1a =ZDV3/3TC/NVP 1c = D4T/3TC/NVP

1b=ZDV3/3TC/ EFV 1d = ZDV3/3TC/NVP

TDF/3TC/NVP or EFV selective setting

ABC/3TC/NVP or EFV selective setting

Second-line Regimen (during treatment failure)

ddIa or TDF+ABC+ LPV/r b or SQV/rb or NFV or IND/r

C. Essential steps in initiation of antiretroviral treatment and follow up of patient:

Standardized clinical assessment of patients and, when available immunological, are mandatory at baseline to decide on initiation of antiretroviral therapy. Patients who do not qualify for this have a follow up protocol that monitors disease progression and starts antiretroviral therapy before life-threatening immunodeficiency sets in. Patients qualifying for antiretroviral therapy are thoroughly evaluated at baseline and for the rest of their lives to monitor toxicity, intolerance, response or failure to treatment. Before ART initiation and thereafter patient readiness and adherence to therapy are always assessed and necessary support provided. Opportunistic infections including TB, IRIS, and co morbidities are looked for and managed.

D. ART monitoring:

Schedule follow up visits at monthly intervals to refill medications until week 12 of therapy, and then monthly for adherence counselling and medication refill with nurse counsellor/pharmacy personnel with every 3-month visits with clinician for clinical evaluation and toxicity assessment as per schedule. At each visit clinical assessment covers:

- Symptoms/signs of potential drug toxicities

- Symptoms/signs of OIs
- Adherence
- Weight
- Change in WHO staging
- Laboratory Monitoring: LFT, RFT, CD4 cell count, CBC (WBC with differential, Haemoglobin and platelet), pregnancy test.

E. Definitions of Treatment failure in ART

Table.2: Definitions of treatment failure in adults and adolescents, FHAPCO, 2005

Clinical Criteria	CD4 Cell Criteria (as determined Q 6 months)
•Occurrence of new opportunistic infection or malignancy signifying clinical disease progression 3 months after initiation of ART. This is to differentiate from the immune reconstitution syndrome. **a** Immune reconstitution does not signify treatment failure and opportunistic infection should be treated as usual, without changes in the antiretroviral regimen. •Recurrence of previous opportunistic infection **b** •Onset or recurrence of WHO Stage III conditions, including but not restricted to: o HIV wasting o Chronic diarrhea of unknown etiology o Prolonged fever of unknown etiology o Recurrent invasive bacterial infections o Recurrent/persistent mucosal candidiasis	•Return of CD4 cell to pretherapy baseline or below without other concomitant infection to explain transient CD4 cell decrease.**c** •>50% fall from therapy CD4 peak level without other concomitant infection to explain transient CD4 cell decrease.c **Virologic Criteria** •VL fails to decrease by 1 log at 6-8 weeks, OR •Does not remain < 400 copies/ml after 24 weeks

a Immune reconstitution syndrome (IRS) is characterized by the appearance of signs and symptoms of an opportunistic disease a few weeks after the start of potent antiretroviral therapy in the setting of advanced immunodeficiency, as an inflammatory response to previously subclinical opportunistic infection. It is also possible that this immunological reconstitution may lead to the development of atypical presentations of some opportunistic infections.

b Recurrence of TB may not represent HIV disease progression, as reinfection may occur. Clinical evaluation is necessary.

c If patient is asymptomatic and treatment failure is being defined by CD4 cell criteria alone, consideration should be given to performing a repeat CD4 cell count if resources permit.

Table.3: Definitions of treatment failure in adults and adolescents, FHAPCO, 2007

	Definition
Clinical Failure **a**	New or recurrent WHO stage 4 condition **b c**
Immunologic Failure **d**	• Fall of CD4 count to pre-therapy baseline (or below); • 50% fall from the on-treatment peak value (if known); • Persistent CD4 levels below 100 cells/MM3
Virological Failure	Plasma viral load above 10,000 copies/ml in duplicates after six months on ART.

a Should be differentiated from Immune Reconstitution Inflammatory Syndrome (IRIS).
b Certain WHO clinical conditions (e.g. pulmonary TB, severe bacterial infections), may indicate treatment failure and should be investigated.
c Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, esophageal candidiasis, recurrent bacterial pneumonia) may not be indicators of treatment failure and thus do not require consideration of second-line therapy.
d Without concomitant infection to cause transient CD4 cell decrease. If patient is asymptomatic and treatment failure is being defined by decreased CD4 cell criteria alone, consideration should be given to performing a repeat CD4 cell count before establishing diagnosis of treatment failure.

II. Literature review

Response to ART

Patients due to various factors show different response to ART. Patients may show virologic, immunologic, or clinical response. Of these, the earliest indicator is **virological** success or failure (decrease or increase in viral load). This is followed, often a little later, by **immunological** treatment success or failure (rise or fall in CD4+ T-cell count). **Clinical** treatment failure, if it occurs, usually only becomes apparent much later. First the lab values deteriorate, then the patient. On the other hand, success of treatment may be seen much earlier; many patients suffering from constitutional symptoms rapidly improve on HAART (3,4, 5).

A. Virological response

Virological treatment success is usually understood as being the reduction of viral load to below the level of detection of 50 copies/ml. This is based on the understanding that, the more rapid and greater the decrease in viral load, the longer the therapeutic effect (6, 7, 8). On HAART, viral load declines in two phases. An initial, very rapid decrease in the first few weeks is followed by a slower phase, in which plasma viremia declines only slowly. Virologic failure is when viral load above the level of detection after six months of treatment or if a rebound in viral load is confirmed (9). Numerous studies indicate that replication and therefore development of resistance can continue even with an undetectable virus load. The good news is that morbidity and mortality may be lowered significantly even if the viral load is not decreased below the level of detection (4, 10, 11). A large cohort study has shown that CD4+ T-cells do not drop as long as the viral load remains below 10,000 copies/ml (12). The most important risk factors for virological treatment failure are extensive pre-treatment with antiretroviral drugs (pre-existing resistance mutations) and non-adherence (11,13,14,15).

B. Immunological response

Immunological treatment success is generally defined as an increase in the CD4+ Tcell count. A more precise definition for immunological treatment success does not currently exist. Depending on the study, increases *by* 50, 100 or 200 CD4+ Tcells/µl or increases *to* above 200 or 500 CD4+ T-cells/µl are defined as success. Failure is usually described as the absence of an increase or as a decrease in the CD4+ T-cell count in patients receiving HAART. It is difficult to individually predict the immunological success of therapy for patients on HAART, as it varies significantly from one person to another. As with the decrease in viral load, the increase in CD4+ T-cell count also occurs in two phases. After a first, usually rapid increase over the first three to four months, further increases are considerably less pronounced. In a prospective study involving some 1,000 patients, the CD4+ T-cell count increased during the first three months by a median of 21.2 CD4+ T-cells/µl per month; in the following months the increase was only 5.5 CD4+ T-cells/µl (15). It is still under debate whether the immune system is restored continuously after a long period of viral load suppression or whether a plateau is possibly reached after three to four years, beyond which there is no further improvement (16, 17, 18). The lower the CD4+ T-cell count at baseline, the less likely it is to normalize completely (19, 20, 21). In the Swiss Cohort, only 39 % of 2,235 patients who had begun HAART in 1996-97 reached a CD4+ T-cell count above 500/µl (21). However, it appears that the introduction of therapy within the first 3-6 months provides certain clues as to how well the immune system will be restored (20). Immunological treatment success is not necessarily linked to maximal viral suppression; even partial suppression can result in improved CD4+ T-cell count (3, 10, 22). The initial level of viral load is also not significant; what seems to be decisive is that the viral load remains lower than before treatment (3, 23). Significant drops in CD4+ T-cell count were observed in patients with a suppressed viremia who switched to a simplified

regimen of ddI and tenofovir plus nevirapine (24). The reason for this seems to be related to negative interactions between ddI and tenofovir. In another study, the CD4 increase on abacavir+3TC was significantly better than on AZT+3TC (both combined with efavirenz), despite comparable virological success. This may be related to the myelotoxicity of AZT (25). Once CD4+ T-cells have normalized and plasma viremia remains undetectable, it is unlikely that they will reduce significantly (26).

C. Clinical response

Clinical treatment success is dependent on virological and immunological therapeutic success. In individual patients, clinical response is not always easy to assess. Clinical success is almost always evaluated via clinical endpoints (AIDS-defining illnesses, death), although the improvement on HAART in a patient with considerable constitutional symptoms should also be seen as clinical success. With regard to risk of disease progression, the immunological response is at least as important as the virological response (3, 27, 28).

Clinical failure is usually defined as the development of an AIDS-associated condition or even death. However, illness is not always indicative of clinical treatment failure. This is particularly true for the immune reconstitution inflammatory syndrome (IRIS), where a pre-existing, subclinical infection becomes apparent during the first weeks following initiation of antiretroviral therapy. On the other hand, if a patient develops serious side effects or even dies, this should clearly be regarded as treatment failure. Many severe, life-threatening events that affect HIV infected patients on HAART today are associated neither with HAART nor AIDS (29).

In many areas, the incidence of AIDS has been reduced to less than a tenth (30). In patients who are continuously followed in specialized centers, AIDS has become a rare occurrence. The mortality rate has continued to decline over time (31). In the Euro- SIDA Cohort, the risk of

suffering or dying from AIDS in the years 1998-2002 was half that of 1996-1997 (32). The Swiss cohort also showed that the effect of HAART increases over time after more than two years on HAART, the risk of disease progression was only 4 % of the risk without HAART (34,35,36). In the SV14604 Study involving 3,485 patients, the frequency of AIDS and death was reduced by about 50 % in the group receiving AZT+ddC+saquinavir hard gel, compared to the groups on dual therapy (37).

According to a more recent investigation, the effect on the individual AIDS diseases appears to be different: the most obvious is the decline in the incidence of viral OIs, although this is not so pronounced for fungal infections (38).

D. Lost to follow Up/drop/discontinued

Due to different reasons significant number of patients lost to follow up or discontinued their treatment. This numbers are especially high in developing countries. Reports from Ethiopia have indicated that about 20% of those started on ART lost to follow UP. Since January 2005, 97,258 people put on ART as of end of June, 2007. Of the total patients who have started ART 72, 884 of them are currently alive and on treatment. Around 24,374 people are not currently following their drugs. As the regional data indicates 12,685 (13.1%) people were defaulted or lost/drop from treatment, 5731(5.9%) deaths were reported so far and 140 people stopped treatment in consultation with physicians. However, the status of 6100 people is not known. The highest drop out rate were recorded in five major regions where 90% of patients getting the services - Addis Ababa (40%), Amhara (22%), Oromia (15%), SNNPR (7%) and Tigray (8%). In Ethiopian National Deference Forces, as of September 2008, about 5692 patients started on ART, of this only 3279 are currently on ART. The others are (116) lost, (215) drop and (142) dead (39).

When to start ART

The regenerative capacity of the immune system in older patients is significantly reduced (45, 46), this has not been acknowledged in any guidelines to date. More importantly, the risk of developing opportunistic infections also depends on age (47). The CASCADE Study (47) exemplifies this: a 25 year-old patient with 100 CD4+ T-cells/µl and a viral load of 100,000 copies/ml has a risk of approximately 10 % for developing AIDS within six months. For a 55 year-old, this level of risk is reached at 150 CD4+ T-cells/µl and a viral load of 30,000 copies/ml. It is also important that not only the absolute CD4+ T-cell count is considered, but the percentage value too. In particular, when the CD4 count is high and the immune status appears good, the CD4 percentage is the most important parameter for predicting the risk of developing AIDS. In one study, the risk of progression for patients with more than 350 CD4+ T-cells/µl was increased approximately four fold, if the percentage of CD4+ T-cells was below 17 % (48).

Determinant factors of response to ART

Various studies have identified different determining factors of response to ART which are related to the base line values, the type and regimen of ARV drug, adherence, the patient socio-economic and demographic factors, other concomitant disease and related conditions.

A. Base line characteristics or Values (CD4 T-cell count, immune status, pre-ART exposure to ARVs, Clinical condition or stage and others)

Large cohorts repeatedly attempt to prove that the starting time point influences virological or immunological treatment success. Factors like base line CD4 cell count, pre –ART exposure to ARV, immunologic status and compliance are associated with the responses.

Many cohort studies have clearly demonstrated that virological response is poorer if the CD4+ T-cell count at initiation of treatment was low and the viral load high (15,55,56,57). It is usually said that the higher the viral load and the lower the CD4+ Tcell count, the less the virological success of HAART. However, in contrary to defenders of an early initiation of HAART, two large cohorts in which only treatment naïve patients were studied doesn't support it (14,62). In the French APROCO Cohort, in which greater differentiation existed between treatment-naïve and treatment-experienced patients (63), treatment-naïve patients with a high viral load at baseline showed at most an insignificant negative trend. That viral load and CD4+ T-cell count have predictive values in all cohort studies in which most (up to 91 %) patients included were usually pre-treated with NRTIs, indicates one thing above all: virological success of HAART may be compromised in patients with prolonged mono or dual therapy. Previous nucleoside analog therapy has been a risk factor for virological treatment failure in many cohorts (15, 55, 59, 60). In the HOPS Cohort, lack of prior therapy was decisive particularly for long-term treatment success (64). This is particularly important in PMTCT served women's. Other factors for the relative risk of virological failure were increased in patients with substantial immunosuppression (below 50 CD4+ T-cells/µl) or very high viral load and compliance. Adherence was an important and even decisive predictor in the few studies in which it has been investigated (15, 65, 66). If these aspects are considered, the issue of whether virological response is really poorer with less favorable baseline values becomes less clear-cut. Even a patient with high viral load and a very low CD4+ T-cell count can potentially control infection quite successfully (67).

Immunological response: Multiple factors influence the increase in CD4+ T-cells: duration of immunosuppression, age, thymus size or extent of thymus degeneration (63). Studies showed that the rise in CD4+ T-cells is similar, although levels remained lower if the CD4 count was

initially low. Furthermore, in some experience immune reconstitution is rarely complete if values were low initially; the more damaged the immune system, the less likely a complete recovery in the long run (68). In the Swiss Cohort, having a low CD4+ Tcell count at baseline was a clear risk factor for not attaining 500 CD4+ T-cells/µl after four years (20, 69). Numerous studies suggest that qualitative immune reconstitution does not initially occur at the same pace as quantitative reconstitution ((70,71,72, 73).

Most studies have found a clear correlation between CD4+ T-cell count at initiation of HAART and rates of both AIDS and death (10, 13, 49, 74). Above all, if the CD4+ T-cell count is below 50/µl when starting therapy, the risk for developing AIDS remains permanently high (65). In other cohorts, the risk remained elevated even below a CD4+ T-cell count of 200/µl (74, 75). The CD4+ T-cell count at the start of treatment correlated highly with the probability later in the course of the illness of AIDS or death (49). Viral load at baseline was only relevant if it was at a very high level, i.e. above 100,000 copies/ml (67).

Studies on the base line value also identified significance association among advanced disease stage, lower baseline CD4 T cell count and longer duration of HIV infection with poor immunologic and clinical responses (49, 76).

A retrospective chart review of 235 HIV-infected Native Americans receiving services at an urban medical center, providing 782.7 person-years of follow-up, to identify determinants of survival reviled that the use of HAART therapy and CD4 count was the strongest predictor of survival from time of AIDS diagnosis. The main outcome measures were time from study entry and from incident AIDS diagnosis to death. Death rates fell from 18.4 (13.3–25.4) per 100 person-years to 6.4 (4.6–8.8) per 100 person-years (RR 0.35, p _ 0.0001). Factors associated with the greatest reduction in risk of death from time of study entry were current use of HAART, HR 0.13 (0.06–0.30, p _0.001), and CD4 count _200 at entry, HR 0.16 (0.08–0.35, p

_ 0.001). Earlier diagnosis and access to effective medical treatment will be key factors in reducing disparities in health brought about by HIV infection in Native American/Alaska Native communities (77).

Other Study of Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy, that is longitudinal CD4 T cell count was analyzed in 293 participants of the Swiss HIV Cohort Study who had had a plasma HIV-1 RNA load <1000 copies/mL for > or =5 years. Determinants of incomplete responses and clinical events were evaluated using logistic regression and survival analyses. The results showed: the median CD4 T cell count increased from 180 cells/microL at baseline to 576 cells/microL 5 years after ART initiation. A total of 35.8% of patients were incomplete responders, of whom 47.6% reached a CD4 T cell plateau <500 cells/microL. Centers for Disease Control and Prevention HIV-1 disease category B and/or C events occurred in 21% of incomplete responders and in 14.4% of complete responders (P>.05). Older age (adjusted odds ratio [aOR], 1.71 per 10-year increase; 95% confidence interval [CI], 1.21-2.43), lower baseline CD4 T cell count (aOR, 0.37 per 100-cell increase; 95% CI, 0.28-0.49), and longer duration of HIV infection (aOR, 2.39 per 10-year increase; 95% CI, 1.19-4.81) were significantly associated with a CD4 T cell count <500 cells/microL at 5 years. The median increases in CD4 T cell count after 3-6 months of ART were smaller in incomplete responders (P<.001) and predicted, in conjunction with baseline CD4 T cell count and age, incomplete response with 80% sensitivity and 72% specificity. Individuals with incomplete CD4 T cell recovery to <500 cells/microL had more advanced HIV-1 infection at baseline. CD4 T cell changes during the first 3-6 months of ART already reflect the capacity of the immune system to replenish depleted CD4 T lymphocytes (20).

Analysis of prospective studies also reviled CD4 base line and at 6 months and plasma viral load of >100,000 copies/ml after 6 months of treatment, cell count has been considered one of the most important variables for predicting response to antiretroviral treatment: The lower the count before treatment is started, the higher the risk that treatment will fail. European researchers now suggest that the CD4 cell count at 6 months into treatment is a substantially more powerful prognosticator than is the nadir count. More than 9000 HIV-infected patients at all stages of disease were monitored after beginning their first course of combination antiretroviral drugs. Patients were followed for at least 6 months (13,408 person-years of follow-up) in 13 separate European and North American cohorts. Nadir count was associated strongly with progression to AIDS or death in a crude analysis, but it was no longer an independent predictor when 6-month CD4 cell count was included in the analysis. Prognosis was poorest for patients with 6-month CD4 cell counts of $<25/mm^3$. These findings provide statistical backing for the frequent clinical observation that patients who show brisk rises in CD4 cell count after beginning antiretroviral therapy tend to do better than do those with sluggish responses, even if nadir CD4 cell counts are similar. This evidence should give patients an additional impetus to adhere to their drug regimens early in treatment (78).

B. ARV type, ART regimen and adherence

Nucleoside-only regimens and poor adherence are known to associate with treatment failure. Retrospective analysis was conducted of HIV-infected patients followed in an urban HIV clinic with an HIV RNA measurement ≤400 copies/mL on ART between January 1, 2003, and December 31, 2004. The primary endpoint was treatment failure, defined as virologic failure (≥1HIV RNA measurement >400 copies/mL), unsanctioned stopping of ART, or loss to follow-up. Prior ART adherence and other baseline patient characteristics were determined at the time of the first suppressed HIV RNA load. Predictors of failure were assessed using

proportional hazards modeling. The results were, of 829 patients in the clinic, 614 had at least 1 HIV RNA measurement ≤400 copies/mL during the study period. Of these, 167 (27.2%) experienced treatment failure. Baseline characteristics associated with treatment failure in the multivariate model were: poor adherence (hazard ratio [HR]= 3.44; 95% confidence interval [CI]: 2.34 to 5.05), absolute neutrophil count <1000/mm3 (HR =2.90, 95% CI: 1.26 to 6.69), CD4 count <200 cells/mm3 (HR= 1.90, 95% CI: 1.31 to 2.76), nucleoside-only regimen (HR = 1.75, 95% CI: 1.08 to 2.82), prior virologic failure (HR = 1.70, 95% CI: 1.22 to 2.39) and ≥1 missed visit in the prior year (HR = 1.56,95% CI: 1.13 to 2.16). More than one quarter of patients in a heterogeneous clinic population had treatment failure over a 2-year period. Prior ART adherence and other data readily identify patient characteristics that could trigger specific interventions to improve ART outcomes (79).

C. Patient socio-economic and demographic factors and adherence

Studies have shown that patients characteristics and related conditions like older age, Female, poor socio-economic status, and injection drug use are associated with poor treatment response. On the Swiss HIV Cohort study older age (adjusted odds ratio [aOR], 1.71 per 10-year increase; 95% confidence interval [CI], 1.21-2.43), and longer duration of HIV infection (aOR, 2.39 per 10-year increase; 95% CI, 1.19-4.81) were significantly associated with a CD4 T cell count <500 cells/microL at 5 years and with other factors predicted incomplete responses (20).

AGE

The risks of developing AIDS within six months, as identified in 3,326 patients from the pre-HAART era, depends on deferent factors. The range of individual risk of progression varies widely from 0 to almost 50 %. For a 55 year-old patient with a CD4+ T-cell count of 50/µl and a viral load of 300,000 copies/ml, the risk of progressing to AIDS within the next 6 months was 44.8 %. In a 25 year-old patient with 500 CD4+ Tcells/µl and a viral load of 3,000 copies/ml,

the risk was only 0.3 %. This demonstrates the importance of these parameters for estimating the individual risk and indication for treatment. However, the age of the patients, which according to these data significantly increases the risk of progression, has so far not been included in any of the guidelines (48,67).

D. Concomitant disease conditions, factors that affect drug pharmacodinamics and kinetics and related factors

The above mentioned analysis of prospective studies, other independent risks for poor outcome (defined as new AIDS-related events or death) were age older than 50, HIV acquired through injection drug use, AIDS-related infection or malignancy diagnosed before or in the first 6 months of treatment and plasma viral load of >100,000 copies/mL after 6 months of treatment

Review from Haiti also identifies coinfection with tropical diseases and tuberculosis, along with malnutrition and limited laboratory monitoring of therapy as important determinant factor for response to ART. The one-year survival rate of adults and children with the acquired immunodeficiency syndrome (AIDS), without antiretroviral therapy, has been about 30 percent in Haiti. High rates of coinfection with tropical diseases and tuberculosis, along with malnutrition and limited laboratory monitoring of therapy, may decrease the efficacy of antiretroviral therapy in these countries. Study on the efficacy of antiretroviral therapy in patients with AIDS and without previous antiretroviral therapy who were treated beginning in March 2003 in Port-au-Prince, Haiti showed: during a 14-month period, three-drug antiretroviral therapy was initiated in 1004 patients, including 94 children under 13 years of age. At enrolment, the median CD4 T-cell count in adults and adolescents was 131/ mm3 (interquartile range, 55 to 211/ mm3); in children, a median of 13 percent of T cells were CD4-positive (interquartile range, 8 to 20 percent). According to a Kaplan–Meier survival analysis,

87 percent of adults and adolescents and 98 percent of children were alive one year after beginning treatment. In a subgroup of 100 adult and adolescent patients who were followed for 48 to 56 weeks, 76 patients had fewer than 400 copies of human immunodeficiency virus RNA per milliliter. In adults and adolescents, the median increase in the CD4 T-cell count from baseline to 12 months was 163/ mm3 (interquartile range, 77 to 251/ mm3). In children, the median percentage of CD4 T cells rose from 13 percent at baseline to 26 percent (inter quartile range, 22 to 36 percent) at 12 months. Treatment-limiting toxic effects occurred in 102 of the 910 adults and adolescents (11 percent) and 5 of the 94 children (5 percent)(80).

A review by Christian Hoffmann and Fiona Mulcahy (81, 82) on discordant response also reviled age, base line CD4 cell count, type of regimen and concomitant infections as important factors. Failure to achieve every one of the therapeutic goals; clinical, immunological and virological is referred to as a discordant response. Some patients may have virological treatment success without immunological improvement, continuing to have a very low CD4+ T-cell count despite undetectable viral load (5, 70, 71). In addition to age, the risk factors for a lack of immunological treatment response, despite good viral suppression, include low CD4+ T-cell counts at baseline, as well as having a low viral load at the start of treatment (20, 83). In older patients, immunological response is often only moderate in comparison to virological response. Various studies have demonstrated that the probability of not achieving a rise in CD4+ T-cell count increases with patient age and with progressive decrease in thymus size as detected by CT (5, 84). Patients who are intravenous drug users also have relatively poor increases in CD4+ T-cells compared to other patients (84).Other possible causes for a lack of immunological response despite good viral suppression may be immuno- or myelosuppressive concomitant therapies. Conversely, HAART may be extremely effective immunologically and induce

significant increases in the CD4+ T-cell count, while viral load remains detectable. This can sometimes be observed in children and adolescents (67).

Study from Ethiopia

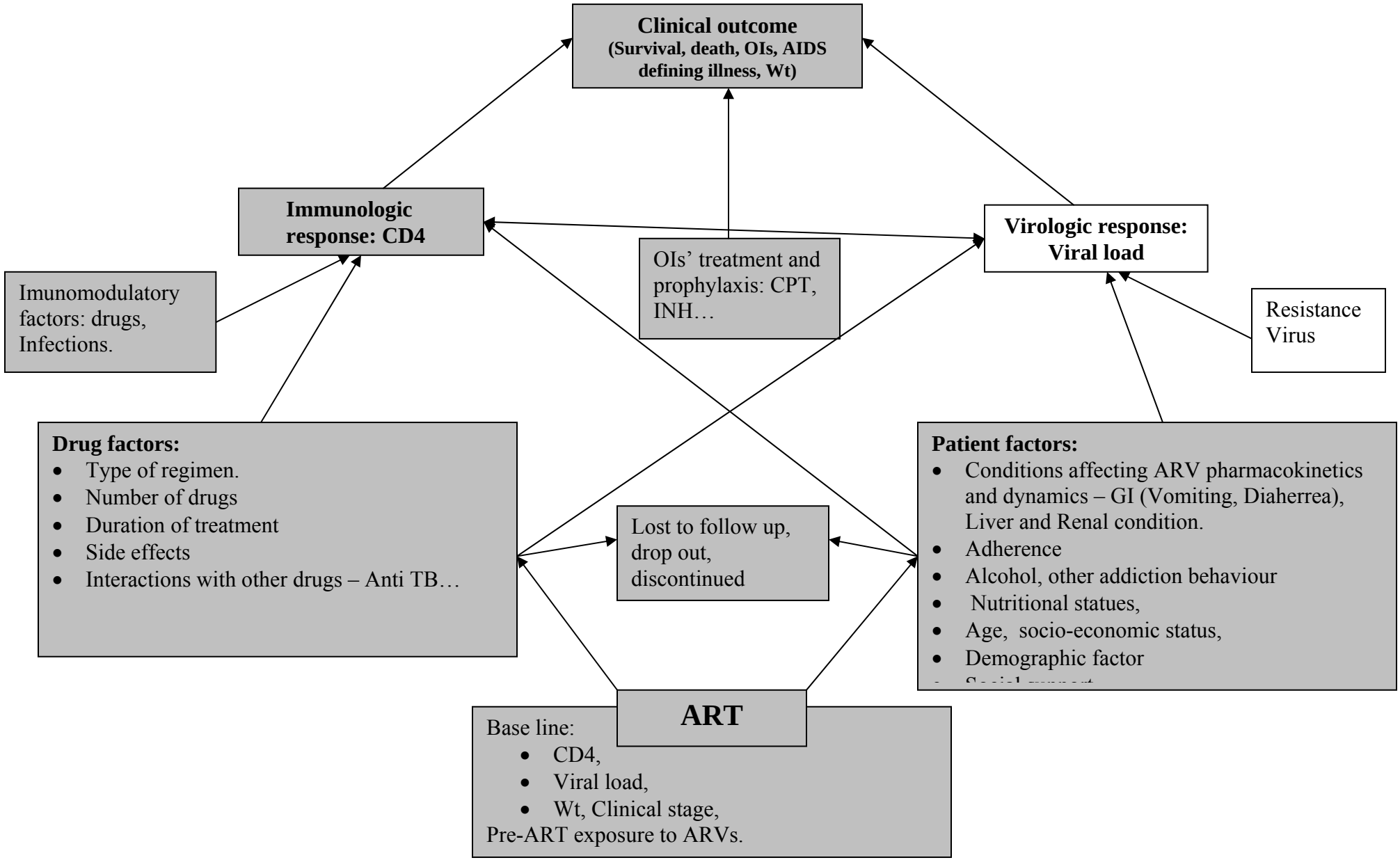
A study at typical Ethiopian district hospital (Arbaminich), found that HAART decreased death and tuberculosis incidence rates in HIV infected Ethiopian patients. Mortality declined by 65% and tuberculosis incidence rate was reduced by almost 90%. Most of the deaths in the HAART cohort occurred within the first three months of therapy. Few patients experienced life-threatening drug side effects. However, both the mortality and the tuberculosis incidence rates are higher in this cohort than in cohorts from the developed world and unfortunately, many of the patients had advanced disease at time of diagnosis. A study using virologic and immunological end points found that HAART was equally effective in African patients and challenged an earlier report that virological failure was more common in Africans while improved survival is encouraging news, it is lower than in the developed world (85).

Although the survival of HIV infected patients has improved following the introduction of HAART, patients in resource-poor countries have higher mortality rates especially during the first weeks of treatment. In the study that examined factors predicting mortality in Ethiopian patients treated with HAART, base line WHO stage, BMI and TLC strongly associated. Out of 162 recruited, 152 treatment-naïve patients contributed 144 person-years of observation (PYO). 86 (57%) of them were men and their median age was 32 years. The overall mortality rate was 16.7 per 100 PYO (24 deaths/144.1 PYO). The highest death rate occurred in the first month of treatment. Compared to the first month, mortality declined by 9-fold after the 18th week of follow-up. Being in WHO clinical stage IV and having TLC<=750/mcL were independent predictors of death. BMI <=18.5 kg/m2 at baseline was associated with death in univariate analysis. Weight loss was seen in about a third of patients who survived up to the fourth week,

and it was associated with increased death. Decline in TLC, HGB and BMI was associated with death in univariate analysis (86).

Unpublished Quality assessment study on the three defense hospitals namely AFTGH, Bella and Debrezeit Air force hospitals reviles that significant change was seen at CD4 count and weight of clients after initiation of ART at six months($p<0.001$). The mean CD4 cells/mm3 before and after ART was 105.6 and 234.5 (SD ±70.6 and 120.7) respectively, and the median CD4 count before initiation of ART was 93cells/mm3, while after treatment at six months increased to 219 cells/mm3 . The 50 %of clients before ART weigh between 61(the 75 percentile) and 49(the 25 percentile), while after ART weigh between 66(the 75 percentile) and 55, the 25 percentile (87).

Figure.1: Conceptual framework of determinant factors of response to ART



III. Rationale/relevance of the study

Patients respond to ART differently and their outcomes are affected by various factors. We also observed variation on the response of patients for ART in the health facilities. Various studies have identified many determinants of response to ART, some studies are inconclusive, and most studies have been conducted in developed countries. In Ethiopia even though the ART program lasts for about 5 years, only few evaluations of outcome and none at Ethiopian defence forces have been completed. The Ethiopian treatment guidelines have not been supported by endogenous studies. Further more, to date there is no study conducted to evaluate the outcome of ART and the determinants for the response in the Ethiopian military.

Identification of the specific determinant factors and evaluation of the outcomes of ART provide help to have full insight on the achievements and challenges of ART program and develop evidence based public health approach of ART. Therefore, this study will support treatment protocols and also helps to see the achievements of the ART program so far in Ethiopian military.

The final outcome of the study also contributes to the country in general and to the national Defence forces health system in particular, to the revision of treatment guidelines, the clinical practice and health system administration and the development of an effective and efficient strategy for better outcome of ART.

It also examines programme factors like adherence, time of initiation of ART, pre-treatment ARV exposure and demographic factors. The results of the evaluation provide the health management system of the Health Department of the National Defence Forces of Ethiopia relevant information on the relationship of key ART programme factor to ART outcome. The

study evaluates the effects of current practice and use as baseline/the background information for further prospective studies.

IV. Objectives of the Study

The general objective was to examine the response of HIV patients to the ART and identify the determinant factors for the response in the Ethiopian military ART facility.

Specific objectives

The study focused in the following specific objectives:

- To describe the patterns of response to ART in HIV patient.
- To evaluate the impacts of ART on the patients survival and immunologic and clinical outcome
- To estimate the time to failure of ART
- To identify the determinants for response to and failure of ART

V. Methodology

Study Design: Historical cohort study of HIV patients who started ART at HIV/AIDS clinic of Bella Defense Hospital, one of the referral hospitals for Ethiopian military health facilities.

Study Area and time: The study was conducted in Bella Defense Hospital, the Ethiopian military hospitals, which is located in Addis Ababa and is used as main referral hospital and the teaching center for the Defense forces, civil servants in the Defense institutions, their families and dependents. The ART clinic serves a diverse patient population from the defense forces, their dependents and retired army. Patients were managed by physicians, health officers, nurse practitioners, the latter two under the supervision or consultation of ART physicians, or by attending physicians alone. Standardized paper charts (National ART recording formats) were used to store records and laboratory results. The records contained information on patient demographics, laboratory, HIV risk behaviors, adherence to ART, medications, and diagnoses, which were entered by data clerks/ ART nurses as part of routine clinical documentation. Laboratory results and appointments were regularly recorded according to the national guideline. Bella Defense ART clinic was supported by University of California San Diego-Ethiopia (UCSD-E). The study covered ART patients who started ART treatment from 05/06/1997E.C to 22/05/2001E.C.

Source Population: The source population for this study was all ART patients of the Defense forces and their family members, civil servants in the Defense forces and their family members.

Study Population: patient started on ART at Bella Defense Hospital and fulfilled the inclusion criteria of the study.

Inclusion Criteria

- On ART regimen that includes at least 3 drugs
- Presence of pre-treatment CD4 cell count.
- CD4 cell count obtained with in the treatment period based on the national guideline.
- Laboratory and clinical data available
- Age 18 years and above.
- Patients started ART at the facility

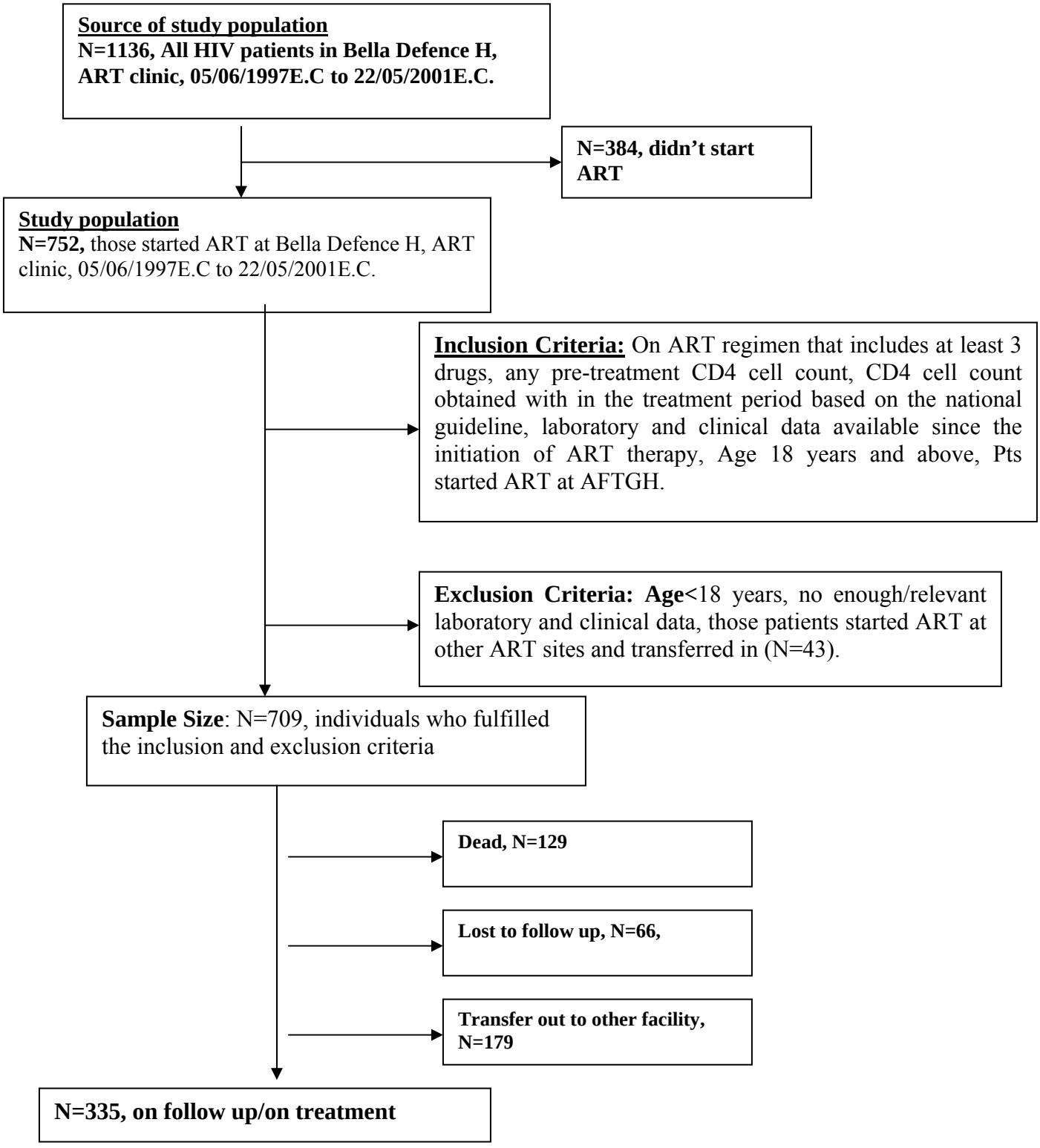
Exclusion Criteria

- With no enough/relevant laboratory and clinical data.
- Those patients who started ART at other ART sites.

Sample size: All ART patients were taken and about 709 adult ART patients who fulfilled the study criteria included. There were about 750 HIV patients on ART during the study period but some of them didn't have adequate data and didn't fulfill the study criteria. Patients who enrolled in the cohort had the following data collected: current age, age at time of ART initiation, gender, education level, literacy, substance use, and ART adherence data, original and current ART regimen, and duration of current ART regimen, CD4 count base line and follow up, disease stage at entry, opportunistic infections, and other co-morbidities. Death and other important events and occurrence of treatment failure were also documented. How ever there were some irregularities or lack of consistency in documentations.

Sampling Procedure/Scheme: (Figure-3)

Figuer.3: Sampling scheme and study follow, Bella Defence Hospital, 2009



VI. Data Collection and Measurement

VI.I. Expected outcome

The study was conducted based on the assumptions of the following dependent and independent variables

The Dependent and Independent Variables

Dependent variables:

- Immunological response – CD4 count (change in the CD4 count over time and failure).
- Clinical response – survival, death, development of OIs or AIDS defining illness.
- Change in therapy – use of 2nd line treatment regimen.
- Weight –change in weight over time

Independent variables:

- Adherence
- Type of regimen
- ARV side effects
- Previous exposure to ARVs
- Base line – CD4, Weight, Hemoglobin, Clinical stage and other patient characteristics.
- Time at HIV diagnosis
- Concomitant infections/situation, immunemodulatory drugs
- Socio-demographic characteristics – Age, Sex, Socio economic characteristics.

Operational definition

- Response failure was occurrence of any of the three outcome immunologic failure, clinical failure, and change to 2nd line drugs.
- Death was any death occurring during ART regardless of the cause excluding accidents and other unrelated.
- Success and failure were according to the national ART guideline definition and criteria (see Introduction)
- Adherence rated according to the national guideline as follows

Adherence % missed doses:

	%	(of 30 doses)	(of 60 doses)
G (good)	>95%	≤ 2 doses	<3 doses
F (fair)	85-94%	3-5 doses	3-9 dose
P (poor)	<85%	≥ 6 doses	>9 doses

VI.II. Data Collectors and their Training

UCSD-E ART data clerks and site data coordinator who were working on filling the ART registers and formats and already had the experience on ART data recording were utilized for this research. And also additional 5 experienced nurses trained and oriented on the data entry and the research questionnaires/formats.

VI.III. Data Collection

Data was collected from each subject using the standard Ethiopian national ART recording formats. For this study secondary data from the national ART registers was collected using the developed questioners. Data management, quality assurance and training were being provided

by the UCSD-E M&E team. The clinical data merged with laboratory data. Clinical data elements included: age, sex, pre-treatment CD4 count and serial CD4 count information, treatment regimen, history of treatment related toxicity, adherence (based on ART clinic and pharmacy records) and HIV disease stage.

VII. Data Management, Analysis, Quality Assurance and Interpretation

Data Coding: - All socio-demographic variables categorized. Numbers identifying variables and appropriate variable name was given. The layout scheme was developed and the codes for each variable identified. Data was entered into and processed using SPSS Version 15. .

Data Entry: Data entry from the questioner was done by the principal investigator. Counter check done at each step.

Data Cleaning: Data were carefully checked for errors before they were analyzed. Frequency tables done and checked for possible outliners and wrong values.. Logical and consistency errors were also checked after completing data entry.

Quality Assurance: there were direct supervision of data personnel on the data collection and cleaning done by the researcher.

Data Analysis

Data was analysed using SPSS, version 15. Frequencies, proportions and summary statistics were used to describe the study population in relation to relevant variables. Socio-demographic subgroups were compared with population characteristics where possible. Therefore, descriptive data listing of demographic and laboratory characteristics was done meticulously. An attempt was made to determine characteristics of patients with end points by

comparing the characteristics of those with and with out response failure. General linear model used for the evaluation of change in the repeated measurement.

Cox proportional hazard model was used to determine the risk of the outcome variables for the determinant factors of the outcome. Kaplan Meier survival analysis to estimate the survival time probability following initiation of ART with and with out determinant variable and Log rank test for comparing survival curves were utilized.

VIII. Ethical Considerations

Ethical clearance for this study was obtained from the ACIPH –Gonder University IRB. Permissions also obtained from Bella Defense Hospital administration.

The study didn't identify individuals or linked to specific groups. Anonymity of the study participants was maintained by omitting names and minimizing other identifying information. Confidentiality of the data also be maintained and only used for this study. Appropriate ethical conduct was maintained throughout the study process and then after during reporting and presentation.

IX. Results

A total of 750 patient records who started ART from 05/06/1997E.C to 22/05/2001E.C were reviewed and 709(94.5%) fulfilled the inclusion criteria and had adequate information and included in the study.

6.1. Socio –Demographic characteristics

Among the participants, 431(60.7%0) were male and 273(38.5%) female. The minimum age was 20, while the maximum was 60. Nearly 75%of the participants were between the age group 20 to 39 and the remaining 40 and above. The mean and median age are 34 (SD=7.629) and 33 respectively.

Majority of the participants were orthodox Christian 581(81.8%) by their religion, married 461(64.9%) and secondary education level 319(44.4%). One hundred sixty one (22.7%) were active military and 233(33.7%) were employed (most of them at NDFE), while 207(30%) were unemployed. Significant number of the participants leaves outside Addis Ababa 310(43.7) at the start ART.

Other social characteristics like disclosure status, 381(53.7) disclosed their HIV status at the start of ART and 167(23.5) had some sort of addiction to tobacco, alcohol, chat or other. Twenty three (8.3% of female) were pregnant at the start or become pregnant during the treatment (Table -4).

Table. 4. Distribution of participants (ART patients) by socio-demographic characteristics, Bella Defence Hospital, 2009. (N=709)

Socio demographic characteristics	Frequency in number	%
Sex(N=704)		
Male	431	60.7
Female	273	38.5
Age(N=707)		
20 - 29	218	30.7
30 – 39	321	45.2
40 – 49	142	20
50 +	26	3.7
Marital status(N=701)		
Never married	137	19.3
Married	461	64.9
Separated	23	3.5
Divorced	35	4.9
Widow/widowed	43	6.1
Occupation(N=690)		
Military	161	22.7
Employed	233	33.7
Unemployed	207	30
Other	89	12.9
Level of education(N=675)		
No education	42	5.9
Primary	263	37
Secondary	315	44.4
Tertiary	65	7.7
Religion(N=679)		
Orthodox	581	81.8
Muslim	45	6.3
Protestant	46	6.5
Catholic	3	0.4
Other	4	0.6
Place of residence(697)		
Addis Ababa and surrounding	387	54.5
Outside Addis Ababa	310	43.7
Disclosure status(N=697)		
Yes	381	53.7
No	315	44.4
Addiction History (Tobacco, alcohol, chat…)(N=683)	167	23.5
Yes	516	72.7
No		

6.2. Baseline characteristics of the study participant

Most of the participants had baseline CD4 cell count 50 and below 211(29.7%) and only 59 patients (8.3%) had CD4 count above 200. The mean CD4 count was 99.15(SD 69.274),

median 87 and the minimum being 1 while the maximum was 427(only one patient), 75% were below 150.

The mean baseline haemoglobin (Normal value >11.5) was 12.11mg/dl (SD 2.35089), minimum 5.1 and maximum 18.2%. The mean liver function test (ALT, Normal value 0 to 50) was 40.1504 (SD=36.55850).The mean weight was 52.0671kg(SD 9.86875) and median 51kg with minimum 24 and maximum 125kg.

Majority of the patient were ambulatory 282(39.7%) and bedridden191 (26.9%) in their functional status. Most of the patient started ART at WHO stage III 372(52.4%) and VI 239(33.7%), and only 96(13.5%) at WHO stage I and II.

About 29(4.1%) already had TB at the start of ART and 167(23.6) on treatment for TB intensive or continuation phase. 20(2.8%) were exposed to some sort of ARV (as treatment or PMTCT).

List of Baseline characteristics of the study participants are in table 5

Table. 5– Baseline characteristics of ART patients, Bella Defence Hospital, 2009

Baseline characteristics	Frequency in number	%
CD4		
0 – 50	211	29.7
51 – 100	186	26.2
101 – 150	138	19.4
150 – 200	115	16.2
>200	59	8.3
Hemoglobin		
<10mg/dl	110	15.5
>=10	556	78.3
Functional status		
Working	218	30.7
Ambulatory	282	39.7
Bedridden	191	26.9
WHO stage		
Stage 1 and 2	96	13.5
Stage 3	372	52.4
Stage 4	239	33.7
ARV exposure		
Yes	20	2.8
No	689	97.0
Past TB treatment		
Yes	291	41

Baseline characteristics	Frequency in number	%
No	416	58.6
TB at the start of ART		
Yes	29	4.1
No	560	78.9
TB treatment at the start		
Yes	167	23.6
No	541	76.2
Liver function		
<=50	508	71.5
>50	135	19

6.3. Treatment and follow up

Majority, 317(44.6) started their treatment with regimen 1a and with 1b 222(31.3%), 127(17.9) with 1d and 41(5.9%) with 1c. Of these 189(26.6%) changed their regimen, but only 116(16.4%) from one regimen type to other, the other were dose adjustment. The main reason for regimen change were side effects/toxicity (74, 63.8%), New TB (27, 23.3%),) and treatment failure (7, 6%).

During the ART 75(10.6%) developed side effects, and 74 necessitates drug regimen change. The regimen associated with side effects were 32 with 1a, 22 with 1b, 15 with 1d and 6 with 1c. The mean time for regimen change was 6.7months (SD=7.791), median 4 months the minimum being 1months and maximum 40months. 30 %(60) of regimen change took place in the first one months and about 70.3 % within the first six months. Regimen change also took place for the second time (53) and third time (9) during the follow up of the patients.

Other important medications documented were INH, Cotrimoxazole and fluconazol as prophylaxis. 666(93.8%) took cotrimoxazol and 6(0.8) are allergic to CTX, only one and two patient took INH and Fluconazol respectively.

It was observed that, the regular follow up schedule according to the national guideline was practiced for most of the patients.

The mean follow up time was 12.5 months (SD=12.062761), Median 8 months (minimum 0 to maximum 40 months). The follow up are 2months, 25% percentiles 8months 50% and 21 months, 75%. Thirty eight (5.4) had adherence problem (fair or poor), and 172(24.2) of the participants adherence status is not recorded.

List of ARV regimen and treatment related conditions are listed in table 6.

Table 6 - ART regimen and treatment follow up outcomes, Bella Defence Hospital, 2009

ARV Drugs and other treatment	Frequency in number	%
Original regimen (N=708)		
1a	317	44.6
1b	22	31.3
1c	41	5.9
1d	127	17.9
Regimen change during the follow up		
Yes	189	26.6
No	518	73
Reason for Regimen change(N=187)		
Side effect	74	39.6
Pregnancy	3	1.6
New TB	27	14.4
New drug available	1	0.5
Drug out of stoke	4	2.1
Clinical failure	3	1.6
Immunologic failure	4	2.1
Other	72	38.5
Occurrence of side effect		
Yes	75	10.6
No	633	89.2
Regimen associated with the Side effect(N=75)		
1a(N=317)	32	42.7(10.1)
1b(N=222)	22	29.3(9.9)
1c(N=41)	6	8(14.6)
1d(N=127)	15	20(11.9)
Cotrimoxazol prophylaxis		
Yes	666	93.8
No	33	4.6
Allergic	6	0.8

6.4. Patterns of response to ART

Patterns of response to ART are described in current status of the patient, the occurrences of important events/outcomes and change over time in repeated measurements of important patient laboratory and clinical values.

6.4.1 Current status and important outcomes

Of the 709 who had started ART in the facility 129(18%) died, 66(9.3) lost to follow up, 178(25.2%) transferred out to other facility and 335(47%) were on follow up (on treatment). During the follow up there were 61(8.6%) new TB, 8(1.1%) new OIs, and 75(10.6%) recorded major side effects.

In about 116(16.9%) of the participant fall in CD4 count occurred but only 47(6.6%, 11.1% if the denominator is those who had more than one visit/record), full fill the national CD4 failure criteria.(any decrease from the baseline or decrease by more than 50% from the follow up peak or persistent low CD4 count below 100). Over all 169(23.8%) responses is failure either due to death, failure in CD4 count or clinical failure or both (Table 7).

Table 7 –Response/outcome description of ART patients, Bella Defence Hospital, 2009

Outcome description	Frequency	%
Current status of the patient (N=709)		
On treatment	335	47
Lost to follow up	66	9.3
Transfer out	179	25.2
Dead	129	18
Stop	1	0.1
Occurrence of important outcomes		
New TB	61	8.6
New OI	8	1.1
Side effects	75	10.6
TB treatment	198	27.9
CD4 fall	116	16.3(if the denominator are those >1record,24.4)
CD4 failure	47	6.6(if the denominator are those >1record,11.1)
Adherence problem		
Yes	38	5.4
No	492	69.3
Unknown	172	24.2
Outcome failure any type(death,CD4 for clinical failure)		
Yes	169	23.8
No	540	76.2

6.4.2. Change over time

Main outcomes or dependent variables which were determined during the follow up are CD4,heamoglobin,weight,liver function tests ,functional status, adherence, side effects, development of OIs and TB. Quantitative variables that were measured during the follow ups are analyzed for their change over time using general liner model repeated measurement.

CD4 cell count

The mean CD4 count change observed over time were high in the first six months that is 117, and 27 and 63 cell/mm3 subsequently in the next two six months. The marginal mean of CD4 count change over time is seen in Figure 4 below.

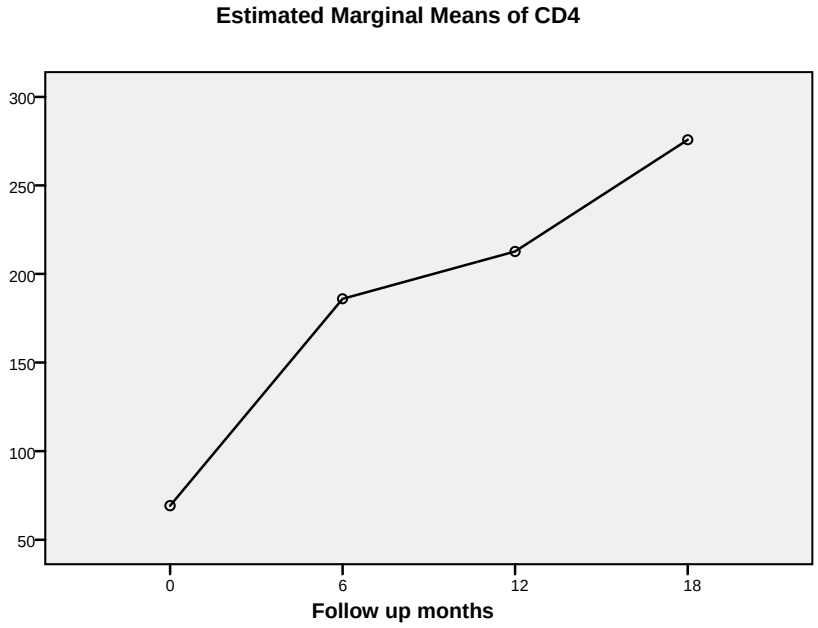


Figure - 4. Trends of CD4 T-cell/mm3 mean estimate in ART patients, Bella Defence Hospital, 2009

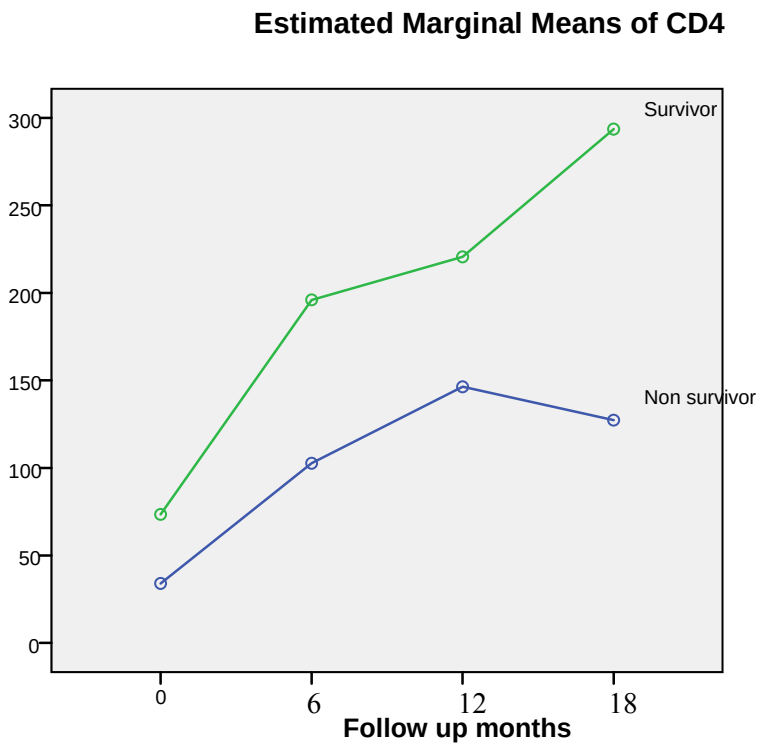


Figure – 5. Trends of CD4 T-cell/mm3 mean estimate in two groups (survivor and non survivor) ART patients, Bella Defence Hospital, 2009

The means of CD4 count were 69.21(SD=53.476), 186(SD=94.331), 212.68(SD=112.757), and 275.75(SD=134.995) in 0, 6, 12, and 18 months of follow up respectively. The mean differences were significant at 0.05 level.

Weight

Using general linear model repeated measurement, the mean change or increases in weight were highest during the first six months. The figure below shows the mean change of weight through the follow up.

The means of weight were 53kg (SD=12.46595), 58.3kg(SD=10.20543), 59.6kg(SD=10.77592), 58.7kg(SD=10.69056), 58.4kg(11.14218),and 58.5kg(SD=11.07745) at

baseline,6,12,18,24 and 30 months respectively. The mean increase was 5.3kg in the first six month and 1.3kg, 0.9kg, 0.4kg and 0.13kg in subsequent six months measurement. The mean difference are significant for the first three six months at 0.05 level.

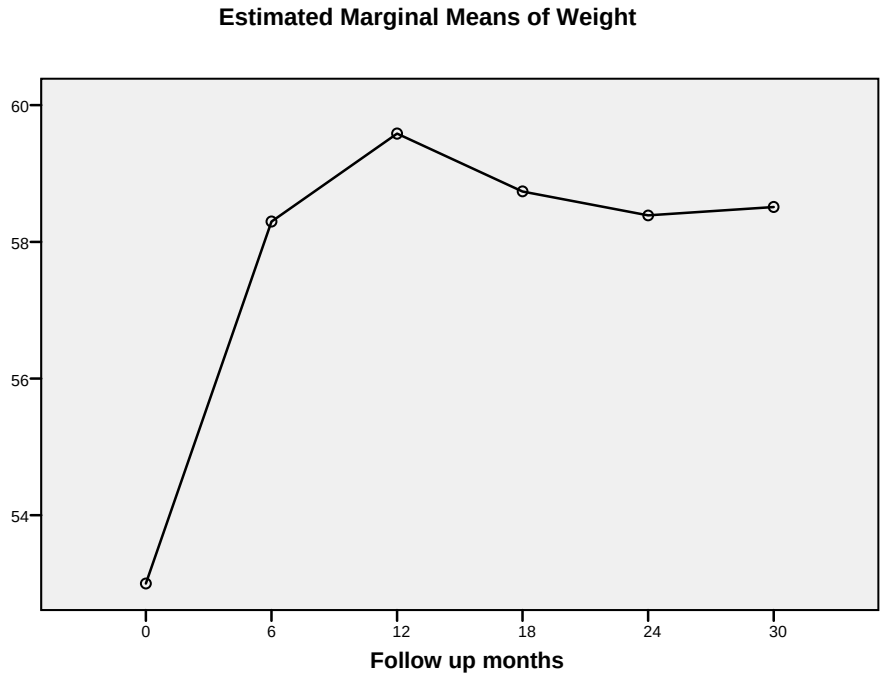


Figure – 6. Trends of Weight of patients (in Kg) mean estimate in ART patients, Bella Defence Hospital, 2009

Haemoglobin and liver function test

The mean haemoglobin change from the base line was high in the first two six months and then after decrease. The mean haemoglobin was 12.1mg/dl (SD=2.56411), 13.8mg/dl (SD=1.98259), 14.9mg/dl (SD=1.84543) and 14.1mg/dl (SD=2.70369) at the base line, 6, 12 and 18 months respectively (Figure -7).

The mean Liver function test (ALT) was 44.5(SD=40.19895), 34.6(SD=20.82413) and 30.1(SD=18.22943) at base line, six months and one year. The general linear model repeated measure mean curve shows a decrease in mean ALT level in the 12 months follow up. Even though the records are few, it shows continuing decrease in the mean ALT value in the 24 months follow up. The following figure shows the trend (Figure 8).

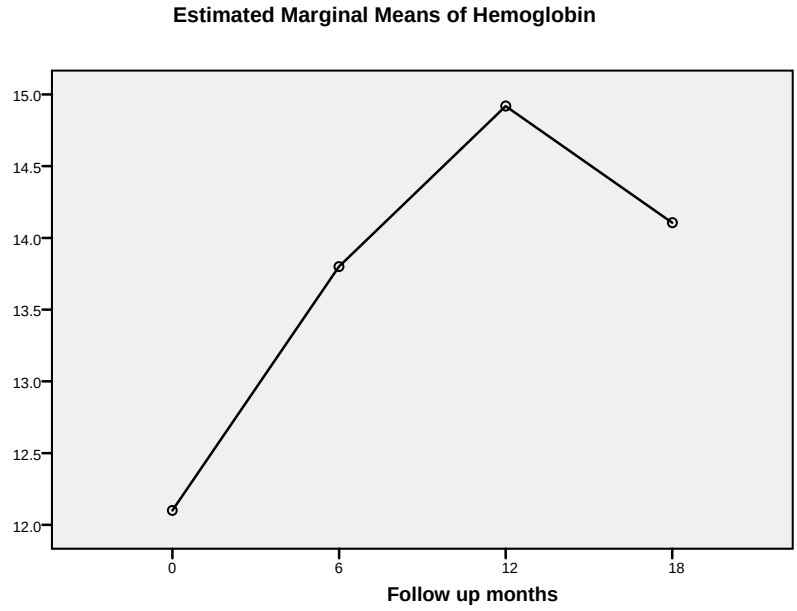


Figure –7. Trends of Hemoglobin mg/dl mean estimate in ART patients, Bella Defence Hospital, 2009

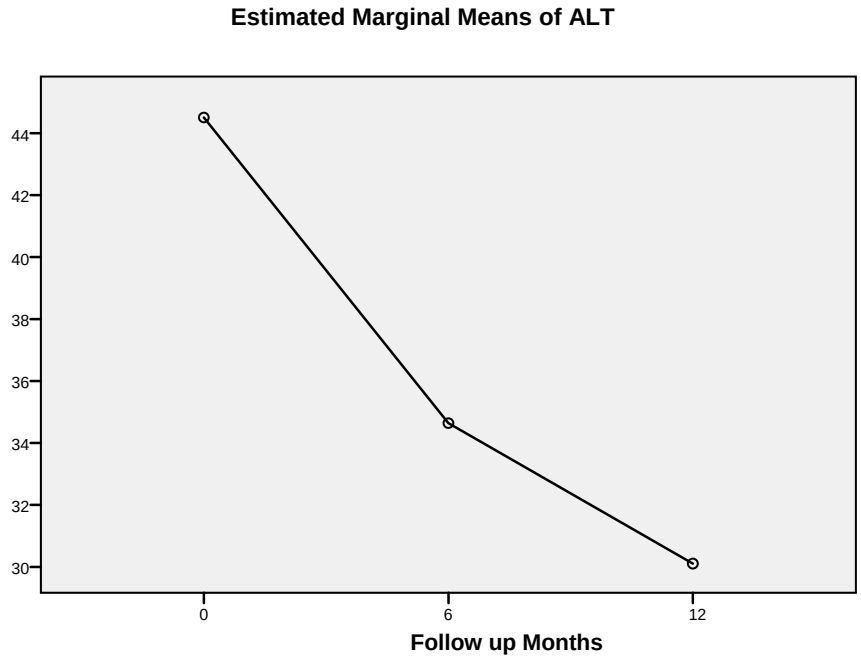


Figure –8. Trends of Liver function test (ALT) mean estimate in ART patients, Bella Defence Hospital, 2009

Functional status

More study subjects had functional status of ambulatory (40.8%) at the start and working (64.4%) at six and subsequent follow up. The proportion of those bedridden decreased from 27.1% to 3.2% at six months.

Table:8.Proportion of functional status during the follow up, Bella Defence Hospital, 2009

Functional status	0 month	3 month	6 month	9 month	12 month	18 month	24 month	30 month	36 month
Working									
Frequency	218	252	284	246	234	189	148	99	55
%	31.5	47.7	64.4	73.2	78.8	87.1	89.7	91.7	96.5
Ambulatory									
Frequency	282	243	143	82	53	24	14	8	1
%	40.8	46	32.4	24.4	17.8	11.1	8.5	7.4	1.8
Bedridden									
Frequency	191	33	14	8	10	4	3	1	1
%	27.6	6.3	3.2	2.4	3.4	1.8	1.8	0.9	1.8

6.5. Outcome/response failure and Survival status

6.5.1. Description of response failure

There were 169(23.8%) response failure (Death, CD4 failure or clinical failure).The following table shows the different proportion of response failure.

Table 9. Proportion of various types of response failure, Bella Defence Hospital, 2009

Outcome failure due to OIs				Outcome failure due to CD4		Total
				Yes	No	
Yes	Outcome failure due to death	Yes	Count	1	2	3
			% of Total	12.5%	25.0%	37.5%
		No	Count	1	4	5
			% of Total	12.5%	50.0%	62.5%
	Total		Count	2	6	8
			% of Total	25.0%	75.0%	100.0%
No	Outcome failure due to death	Yes	Count	10	116	126
			% of Total	1.4%	16.6%	18.0%
		No	Count	35	539	574
			% of Total	5.0%	77.0%	82.0%
	Total		Count	45	655	700
			% of Total	6.4%	93.6%	100.0%

Description of response failure -any

A total of 709 HIV infected adults starting ART had been monitored from 0 to 40 months with mean follow up time of 12.5 months(SD=12.06276),median 8 months.169(23.8%) are outcome failure. Majority of the failure, 108 (63.9%) occurred during the first 3 months of this 79(46.8%) occurs in the first month of follow up.

The mean survival time estimate for the whole cohort by Kaplan Meir analysis was 29.264 months (95%CI 27.890, 30.637, SE 0.701)

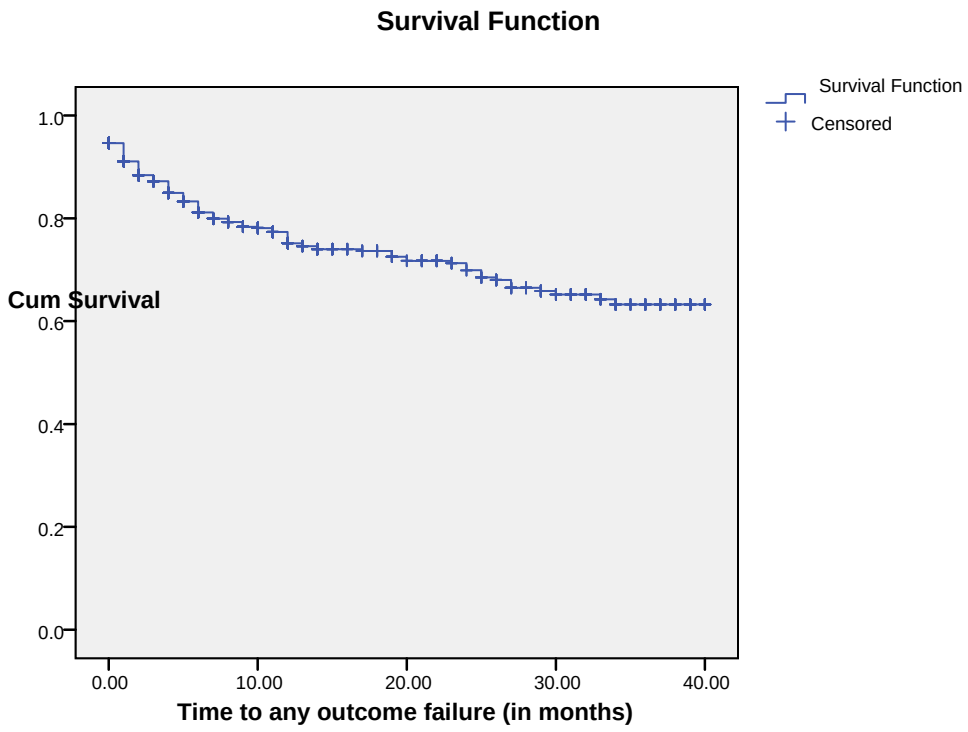


Figure –9. Kaplan Meier Estimates of any outcome failure - free survival in ART Cohorts, Bella Defence Hospital, 2009

Description of outcome failure - death

129(18.2%) died in the cohort. Majority of the death 60(46.5%) occurred in the first one month, and 83(64.5%) in the first three months. The mean survival time estimate for the whole cohort by Kaplan Meir survival analysis was 32.001(95%CI 30.762, 33.240, SE 0.632).

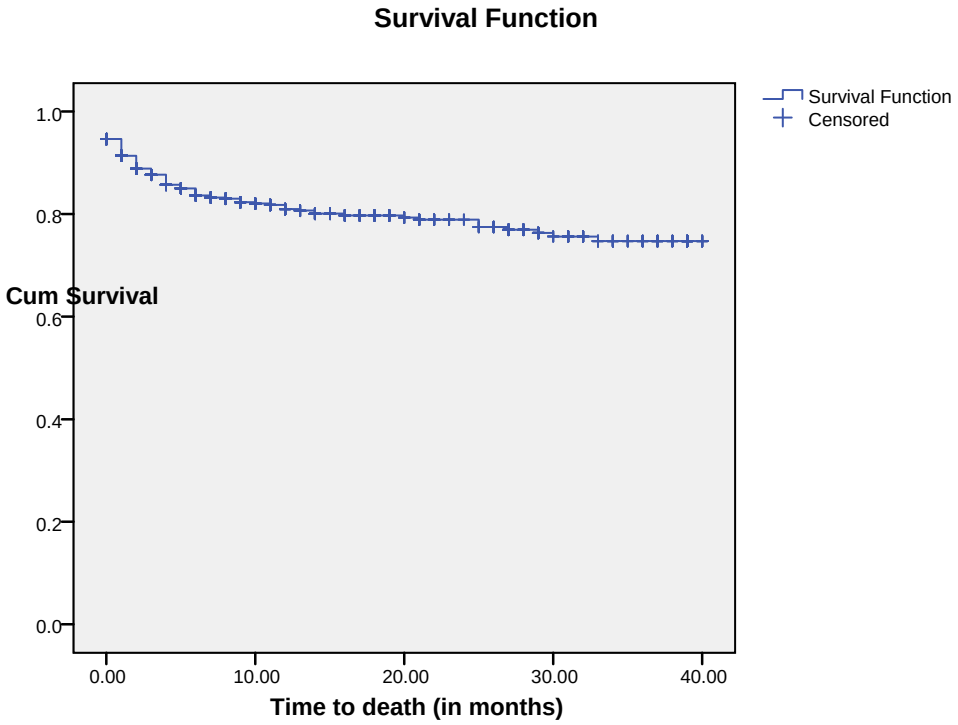


Figure – 10. Kaplan Meier Estimates of survival in ART Cohorts, Bella Defence Hospital, 2009

Description of outcome failure – CD4 failure

47(6.6%) patient experience CD4 count failure during their follow up. The mean time estimate for CD4 failure for the whole cohort was 35.964 months (95%CI 34.883, 37.045,SE 0.552). Majority 30(64%) of the CD4 failure occurs after six months but within one year.

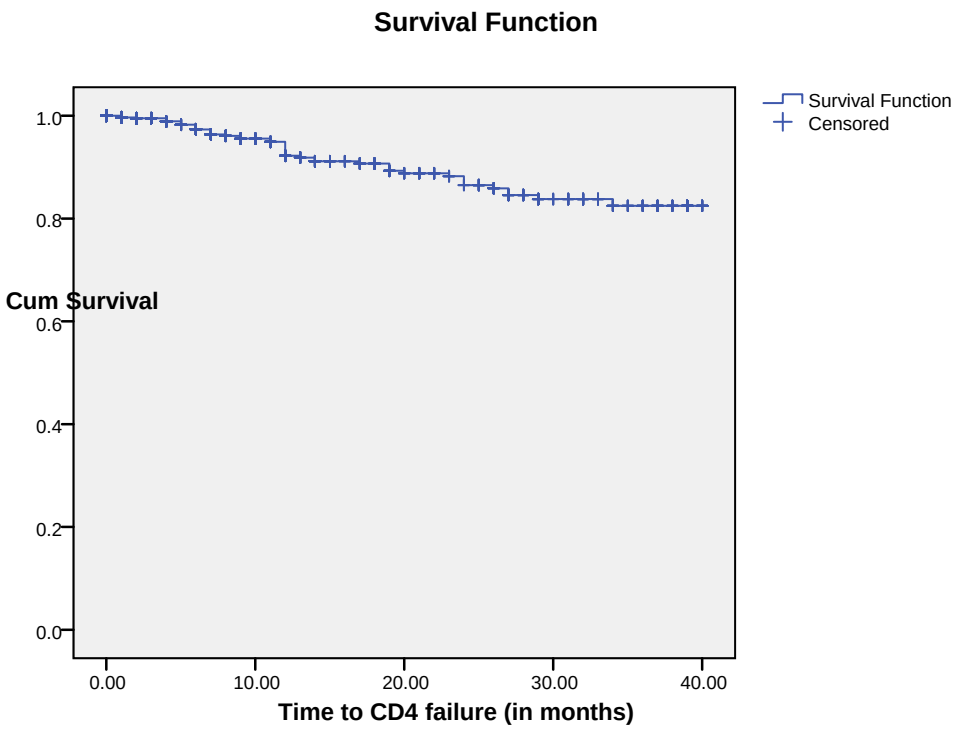


Figure –11. Kaplan Meier Estimates of CD4 failure - free survival in ART Cohorts, Bella Defence Hospital, 2009

6.5.2. Base line characteristics of response failure and non failure – comparison between death and survivor/on treatment group.

The base line values mean comparison using independent sample t-test between those survivor and dead are in the table below. The mean difference in base line Age, CD4 count, Haemoglobin, liver function test (ALT) and weight are statistically significant at the level of P-value 0.05

Table –10. Comparison of mean of baseline characteristics between survivor and non survivor, Bella Defence Hospital, 2009

Variables	Survivor (on treatment)	Non survivor (Death)	Mean Difference	95%CI	P-value (Sig.2 tailed)
	Mean(SD)	Mean(SD)			
Age	34.43(7.483)	36.7(8.425)	2.264	0.589,3.940	0.008
CD4	107.84(70.788)	65.33(54.934)	-42.513	-54.701,-30.326	.000
Hg	12.3389(2.16754)	11.0828(2.29655)	-1.2561	-1.7400,-0.7722	0.000
LFT(ALT)	35.9311(28.3093)	45.6356(41.75584)	9.70453	1.47372,17.93533	0.021
Weight	53.5048(10.62684)	48.8008(8.72380)	-4.70400	-6.62596,-2.78204	0.000

6.7. Determinants for response to and failure of ART

In separate Cox model for determinants of response failure (any failure) being sex male (HR =1.403,95%CI1.015,1.938), age greater than>50 years (HR =2.013, 95CI%1.040,3.898),Base line CD4 count less than 100 (HR =1.916,95%CI1.379,2.662), haemoglobin<10mg/dl (HR =2.276,95%CI1.606,3.234), Functional status bedridden and ambulatory (HR =3.814,95%CI2.446,5.947,HR =1.778 95%CI 1.126,2.809), WHO stage 4 and 3 (HR= 4.140,95%CI 2.006,8.546,HR =2.222,95%CI 1.071,4.611), previous exposure to ARV (HR =2.765,95%CI 1.358,5.633), presence of TB treatment at the start of ART (HR =2.750,95%CI 1.014,7.455),occurrence of side effects (HR=1.976,95%CI 1.306,2.990) and presence of poor or fair adherence problem(HR=5.078,95%CI 3.236,7.971) were associated with response failure. List of independent variables and association with response failure are described in table below.

Table -11. Bivariate Analysis (Cox model) of independent variables for any outcome failure in ART patients, Bella Defence Hospital, 2009

Variables	Number	Number of Event	HR	95%CI	P-value
Sex					
Male	430	**111**	**1.403**	1.015,1.938	**0.040**
Female	273	**55**	**1**		
Age					0.006
20 - 29	217	44	1		
30 – 39	321	64	0.902	0.614,1.325	0.6
40 – 49	142	49	**1.551**	1.032,2.332	**0.035**
50 +	26	11	**2.013**	1.040,3.898	**0.038**
Distance from Bella					
Adds Ababa and surrounding	387	104	1		
Out of Addis Ababa	309	61	0.944	0.687,1.298	0.722
Marital status					0.910
Never married	137	30	0.945	0.632,1.4515	0.785
Married	460	112	1		
Separated/Divorced/Widow/widowed	103	25	0.919	0.565,1.418	0.702
Occupation					0.205
Military	160	29	0.752	0.485,1.168	0.417
Employed/Self employed	228	64	1		
Unemployed	207	56	0.976	0.682,1.398	0.896
Level of education					
No education/Primary	305	71	1.165	0.848,1.601	0.346
Secondary/Tertiary	369	83	1		
Disclosure status					
Yes	381	87	1		
No	314	73	1.073	0.786,1.466	0.655

Variables	Number	Number of Event	HR	95%CI	P-value
Addiction History (Tobacco, alcohol, chat...)					
Yes	167	42	1.244	0.871,1.776	0.230
No	515	109	1		
CD4					
<100	393	118	**1.923**	1.381,2.677	**0.000**
>=100	316	51	**1**		
CD4					
0 – 200	650	158	1.185	0.642,2.184	0.587
>200	59	11	1		
Hemoglobin					
<10mg/dl	110	44	**2.276**	1.606,3.234	**0.000**
>=10mg/dl	556	110	**1**		
Functional status					0.00
Working	218	26	1		
Ambulatory	282	63	**1.778**	1.126,2.809	**0.014**
Bedridden	191	78	**3.814**	2.446,5.947	**0.000**
WHO stage					0.000
Stage 1 and 2	96	8	1		
Stage 3	371	73	**2.222**	1.071,4.611	**0.032**
Stage 4	239	87	**4.140**	2.006,8.546	**0.000**
ARV exposure(other than PMTCT)					
Yes	12	8	**2.765**	1.358,5.633	**0.005**
No	695	161			
TB treatment during the follow up					
Yes	198	61	**1.416**	1.034,1.939	**0.030**
No	509	108	**1**		
TB treatment at the start of ART					0.073
Yes	8	4	**2.750**	1.014,7.455	**0.047**
Intensive phase	108	33	1.431	0.973,2.103	0.068
Continuation phase	51	11	0.948	0.511,1.757	0.864
No	541	121	1		
Weight at the start below mean					
<mean(52.1kg)	375	106	**1.654**	1.199,2.283	**0.002**
>=mean(52.1kg)	324	57	**1**		
Liver function (ALT)					0.428
<= 50	508	116	1		
51 – 100	94	30	0.948	0.497,1.809	0.871
>100	41	10	1.238	0.605,2.533	0.559
Original regimen					0.347
1a (d4t -3TC-NVP)	314	81	1		
1b(drt-3TC-EFV)	223	57	1.271	0.811,1.990	0.296
1c(AZT-3TC-NVP)	42	5	1.353	0.845,2.166	0.296
1d(AZT-3TC-EFV)	127	25	0.694	0.266,1.814	0.457
Occurrence of side effect					
Yes	75	29	**1.976**	1.306,2.990	**0.001**
No	573	99	**1**		
Cotrimoxazol prophylaxis					
Yes	666	158	1		
No	39	11	1.237	0.671,2.281	0.496
Adherence problem					
Yes	38	26	**5.078**	3.236,7.971	**0.000**
No	492	70	**1**		

However in multivariate analysis using Cox model only adherence problem (HR=5.802, 95%CI 3.562, 9.451), previous exposure to ARV (HR=4.220, 95%CI1.664, 10.702), occurrence of side effects during the treatment (HR=2.161, 95%CI 1.321, 3.5350) and patient functional status at the start being bedridden (HR=2.039, 95%CI 1.306, 4.083) are significantly associated with response failure.

Table –12. Multivariate analysis for the variables–Cox model/Final model, Bella Defence Hospital, 2009

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
ARV exposure	1.440	.475	9.199	1	.002	4.220	1.664	10.702
Occurrence of Side effects	.771	.251	9.427	1	.002	2.161	1.321	3.535
Func.working			12.268	2	.002			
Func.ambulatory	.040	.288	.019	1	.890	1.041	.591	1.831
Func.bedridden	.837	.291	8.286	1	.004	2.309	1.306	4.083
Poor/fair adherence	1.758	.249	49.872	1	.000	5.802	3.562	9.451
Sex(male)	.437	.233	3.519	1	.061	1.548	.981	2.443

In other hand when the functional status is out of the model haemoglobin level <10mg/dl at the start of ART (HR=1.703, 95%CI 1.026, 2.829) and sex being male (HR=1.653, 95%CI 1.041, 2.624) are significantly associated with response failure.

Table –12. Multivariate Cox model, functional status is out/final model, Bella Defence Hospital, 2009

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
ARV exposure	1.099	.481	5.224	1	.022	3.001	1.170	7.702
Side effects	.727	.251	8.402	1	.004	2.068	1.265	3.381
Hg<10mg/dl	.533	.259	4.233	1	.040	1.703	1.026	2.829
Poor/fair adhere	1.677	.252	44.155	1	.000	5.349	3.262	8.773
Sex(male)	.503	.236	4.544	1	.033	1.653	1.041	2.624

6.8. Survival analysis's according to the determinants (Adherence problem, ARV-exposure, side effects and functional status, sex and haemoglobin)

Adherence – the mean survival time estimate for those who had adherence problem was 12.757(12.550 – 21.964, SE 2.402) and median 12. And 33.707(32.373 – 35.042, SE 0.681) for those who didn't have adherence problem, Patients with adherence problem had decreased survival by 16months.Probablity of surviving for non adhering patients reaches 50%(40% and 60% for male and female respectively), and 20%(40%and 18% for male and female respectively) in 12 and 40 months respectively. Test of equality of survival distributions for the different levels of adherence problem regroup. The difference in survival time is significant by Log Rank (mantel-Cox) test (P.value =0.000)

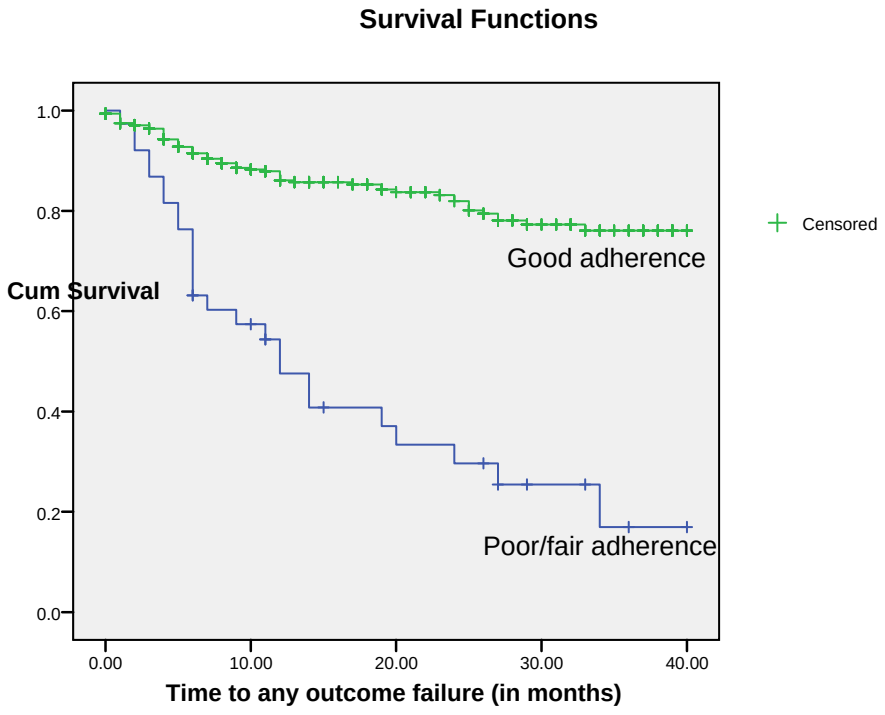


Figure –12. Kaplan Meier Estimates of any outcome failure - free survival in the two (good vs. poor/fair adherence) ART Cohorts, Bella Defence Hospital, 2009

The mean survival time estimate for Pre treatment ARV-exposure 17.375 months (7.649 - 27.101, SE 4.962) and median 4months.But the mean survival time for those who don't have pre –treatment exposure history was 29.514monthes (28.133, 30.896, SE 0.701).pre-treatment ARV exposed had reduced survival by 12months. Log Rank (mantel-Cox) test p-value=0.003

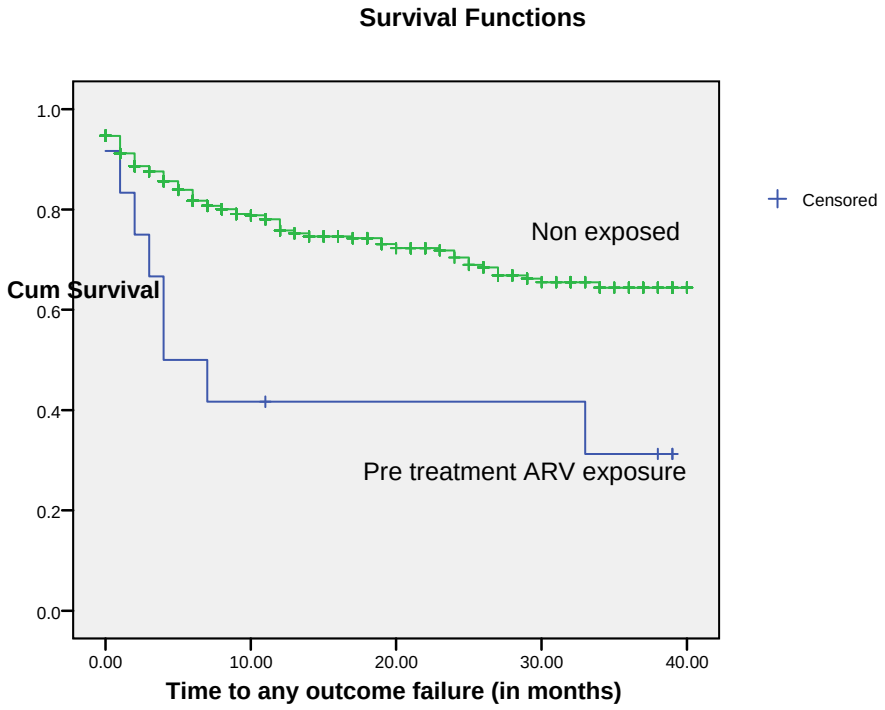


Figure –13. Kaplan Meier Estimates of any outcome failure - free survival in the two (ARV exposed vs. non exposed) ART Cohorts, Bella Defence Hospital, 2009

The mean survival time for those who develop side effects was 25.750 months (21.904-29.596,SE 1.962) and median 27 months. For those who doesn't have side effects the mean survival time was 32.063 months(29.729 – 32.416,SE 0.711).The Log rank(mantle –Cox)test-value =001.But in pair wise Log rank test for sex, it is not significant for females(P-value =0.513)

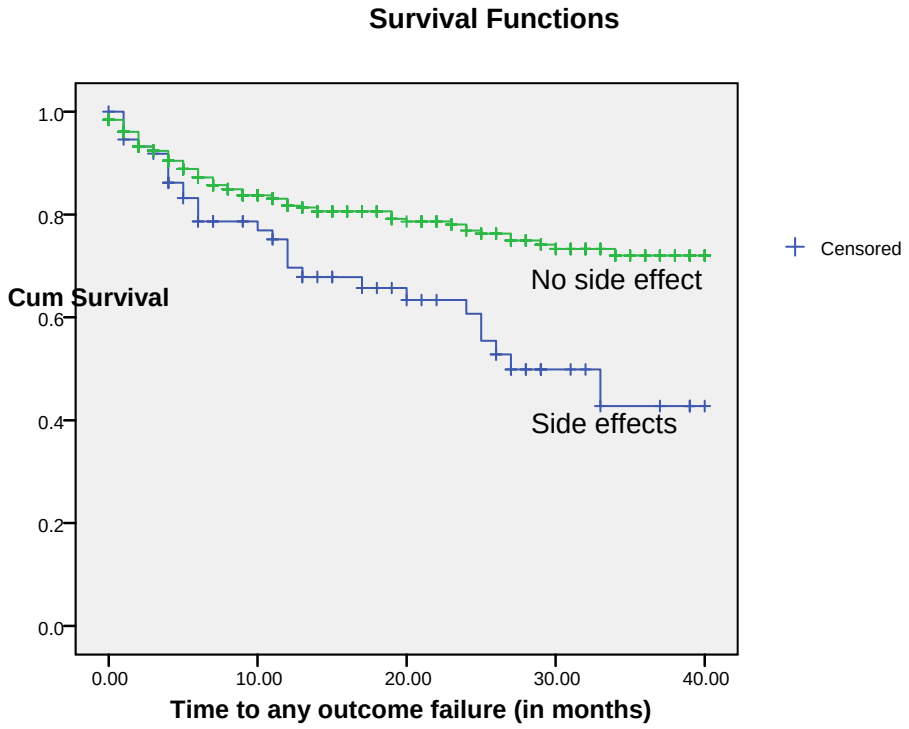


Figure –14. Kaplan Meier Estimates of any outcome failure - free survival in the two (Side effect vs. No side effects) ART Cohorts, Bella Defence Hospital, 2009.

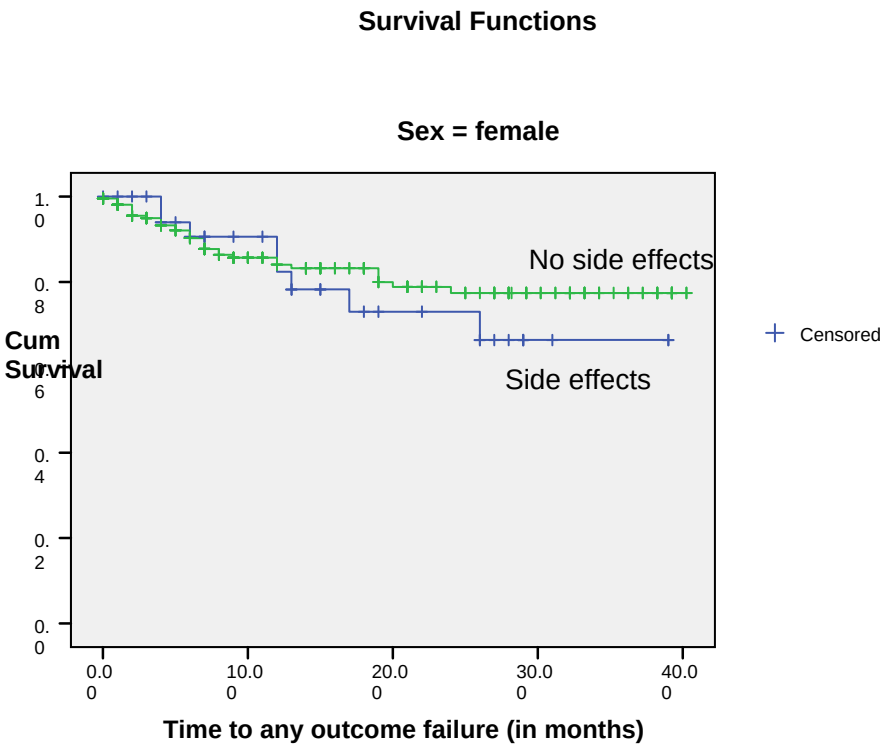


Figure –15. Kaplan Meier Estimates of any outcome failure - free survival in the two (Side effects vs. No side effects) Female ART Cohorts, Bella Defence Hospital, 2009

The mean survival time for those who are male was 28.301 months (26.481 – 30.120,SE 0.928). For those who are female the mean survival time was 31.061 months(28.999 – 33.123,SE 1.052).The Log rank(mantle –Cox)test-value =037.

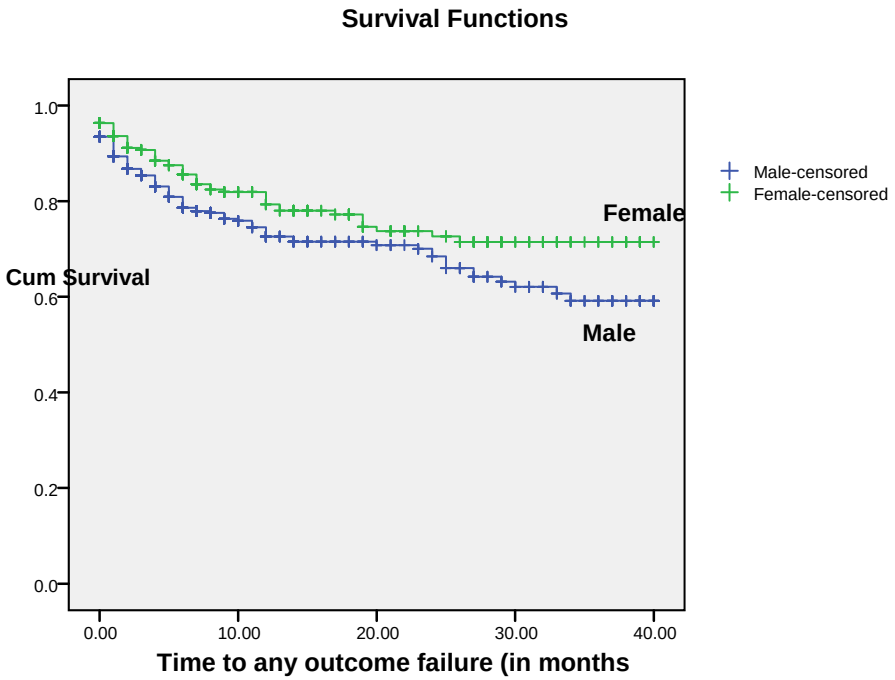


Figure –16. Kaplan Meier Estimates of any outcome failure - free survival in the two (Male vs. Female) ART Cohorts, Bella Defence Hospital, 2009

The mean survival time for ART patients with base line hemoglobin level <=10mg/dlwas 25.299months (22.019, 28.580 SE 1.674), and 30.782months (29.262, 32.301SE=0.775) for those Hg level >10mg/dl.those with Hg<=10mg/dl had reduced survival 5.5months.the mean survival time for working, ambulatory and bedridden functional status were 32.968(30.824 – 35.113,SE =1.094),30.380(28.336 – 32.424,SE=1.043) and 22.607(19.779 – 25.434,SE=1.442) respectively. The difference in survival time is significant (Log Rank test-value=0.000).

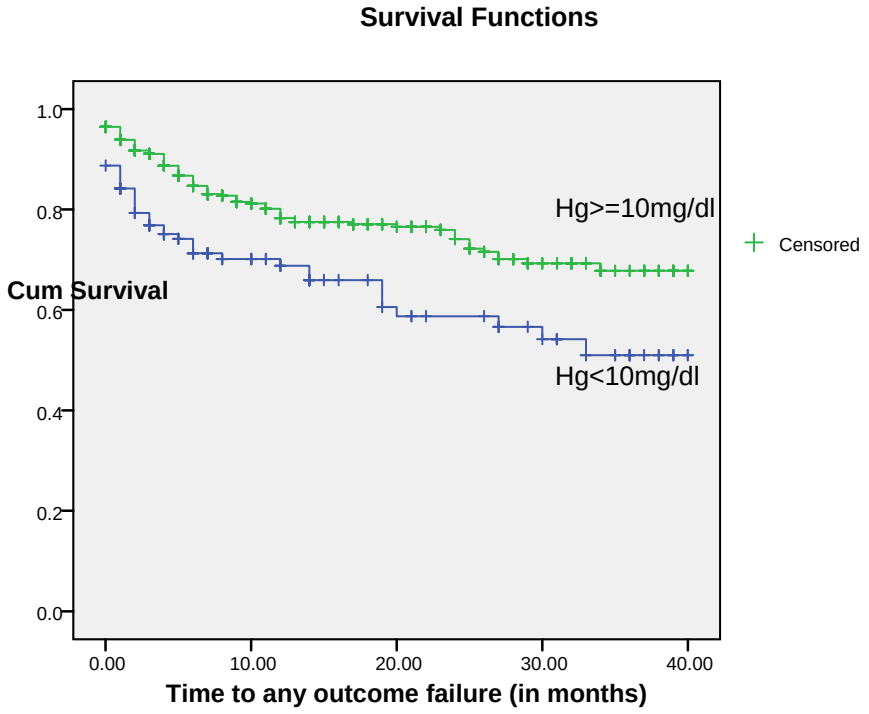


Figure –17. Kaplan Meier Estimates of any outcome failure - free survival in the two (Hg>=10mg/dl vs. <10mg/dl) ART Cohorts, Bella Defense Hospital, 2009

X. Discussion

To my knowledge this is the first study in the Ethiopian military HIV treatment facilities intended to see the patterns and determinants of response to and failure of ART.

In this facility based retrospective cohort analysis of adult HIV infected patients managed under normal programmatic conditions in one of the Ethiopian military HIV treatment facilities, a statistically significant difference was observed in the baseline characteristics of those responded well to and failure of ART. Adherence problem, previous exposure to ARV, occurrence of side effects during the follow up, lower base line haemoglobin level and impaired functional status were independent predictors of response failure of ART.

The majority (60.7%) of study participants were male unlike the national figure where much of the ART beneficiaries and also the prevalence are high in females. This may be due to the fact that Bella Defence referral hospital is providing services for national defence forces of Ethiopia most of its member are male.

Most of the patients start ART at low CD4 count (55% of the participant below 100), advanced clinical stage (33.7%and 52.4% are WHO stage III and VI) and when their function status (26.9% bedridden) was impaired. This is may be due to the criteria for ART initiation or most of the patient especially in the earlier time, presents themselves at later stage and early diagnosis and testing not widely practiced in the health facilities. This was also the case in the national reports and a cohort study done at Arba Minch Hospital (85).

CPT, cotrimoxazole preventive therapy was widely (93.8%) practiced during the follow up; however INH preventive therapy was almost nil. This may be mainly because separate INH drug is not available, TB screening/exclusion of TB was difficult and also in some developing countries health care workers don't believe IPT is beneficiary (80).

Patterns of Response

The patterns of response observed in this cohort study revealed that significant (129, 18%) number of ART patient died. The observed high death rate is also consistent with study from Haiti and in the early era of HAART in developed world (80, 85). In the Tanzanian study with median follow up time of 10.9 months 29.7 %(95) death occurred. The lost follow up also 9.7%(31) for the whole cohort in the follow up time(60.This may also be due to the high rate of death in earlier time/beginning of ART in Ethiopia where most of the patients are late presenter/presented at advanced or end stage . The lost follow rate (9.3%) in the cohort is much lower than the national reports and comparable to the Defence health facility reports and the study in Haiti (80). The transfer out rates are also high (178, 25.2%) in this cohort, it may be because Bella Defence Hospital is the referral hospital and patient comes from every corner for treatment and send back when feel better. most of the transfer out is also for those who live outside Addis Ababa (138, 77.5%). In recent years there were also expansions of ART services in NDFE where patients will be transferred out.

Tuberculosis: the study identified a high occurrence of new TB (61, 8.6%) among the cohort, higher than similar study in Haiti (41, 5%) (80). It may be due to high burden of TB in Ethiopian general population or some other factors like the absence of INH prophylactic therapy in these cohort.

In contrary to our assumption, the presence or diagnosis of TB at the start of ART (29, 4.1%) and the fact that most of the patients were on TB treatment (167, 23.6%) during their ART initiation, the multivariate Cox analysis showed non significant associations with response failure. However, TB treatment especially initiation phase strongly predicts response failure in bivariate Cox analysis. Study from Haiti also identified that there was no significant difference in survival between patients with and patients with out tuberculosis (80).

Side effects: significant number of patients develops side effects (75, 10.6%) and almost all (74) necessitates regimen change. The findings are also consistent with rates of side effects in the Haiti study (102, 11 %(91, 10%).Recent study from developed country demonstrated that people of African decent are at greater risk than others for central nervous system side effects from efavirenz (80). Unfortunately specific types of were not documented in the follow up records where the study conducted and difficult to know the rates of the various types of side effects.

CD4 cell response

In about 116(16.9%) of the participant fall in the CD4 count was observed but only 47(6.6%) full fill the national CD4 failure criteria. The observed CD4 fall may be due to laboratory error, since the 95% CI for a true 100cells/mm3 is 118 to 337cells/mm3 or it is because due to laboratory, seasonal or diurnal variation. The effects of concomitant infection or use of corticosteroids might also bring about fall in CD4 count.

Taking the whole cohort, rapid increment of CD4 count (117cell/mm3) occurs in the first six months and then after slow increment (27 and 63 cell/mm3) in the next two six months. Study from South Africa also demonstrate almost similar finding, that there were rapid increments of median CD4 value (25.5cell/mm3/month) in first four months and then 7.7cells/mm3/month in the next eight months (88). The Haitian study also revealed that the median increments at six months were 128cell/mm3 (80). Studies also showed that the rapid increment phase is not affected by the base line CD4 cell count, even those with CD4 count<50 respond at greater level(88). The finding in this study also demonstrated the same. A thesis on ART service quality assessment at three Defense hospitals also indicated a mean increment of CD4 count by 128.8cells/mm3 at six months of follow up (87)

Weight gain

After the start of ART an increment in mean patient weight observed. The patient had gained a mean of 5.3kg at six month and then 1.3 to 0.4 in the subsequent three six months. Study from Haiti and other three large cohorts for low resource countries also demonstrated comparable findings (80,89).In the Haiti study patient had gained a median of 4kg and in the later three studies a median of 3kg, 5kg and 4kg increment was observed at six months of ART.

The haemoglobin values also showed significant increment in the first 12 months where as the liver function test declines through time. The haemoglobin increment was predictive of treatment success (holding the effects of AZT). The relatively high value of at the start and decline in the liver function test (ALT) through time may be explained by toxic effects at the liver by the high rates of TB and TB treatment at the start of ART.

As a response to the treatment the functional status of the patient improved. The proportion of bedridden patients (27.6%) at the start of ART decreases below 4% at six months. this was might be due to the good response to ART and the presence of 4% at six months may be due to response failure group.

Response failure and its determinants

In this study three types of response failure namely 129(18.2%)death,47(6.6%) failure in CD4 count and 8 (1.1%) clinical failure as defined by occurrence of AIDS defining illness, TB or OIs after three months of treatment. The findings were comparable to other studies in developing countries (80,90), how ever cohort studies from developed and non resource limiting set up demonstrated much lower response failure(91,92).The difference could be early diagnosis and treatment, good patient base line characteristics and socio-demographic factors and also treatment approaches . The study revealed that majority (64.5%) of deaths occurs in the first three months, mostly (46.5%) in the first month. A prospective cohort study in Ethiopia

findings also revealed high mortality in early weeks of treatment (85). The high mortality in the first months of ART may tell the need of close and quality clinical follow at this time.

A statistically significant differences in the mean base line characteristics of the survivor (those on treatment) and non survivor (dead) were found. The differences are the mean age at the start was higher in the non survivor, whereas the mean CD4 count, weight, and haemoglobin were lower. Mean Liver function test (ALT) was higher in non survivor, which may be explained by relatively high proportion of TB treatment (34.1% vs 26.7%) among the non survivor that have toxic effects on the liver or the non survivor may have concomitant liver infection during the initiation of treatment or it may be due to other factors. However the survival is time dependent and base line factors effect changed over time and confounded by different variables, it is unable to label them as predictors of survival or response failure with out further analysis.

The result from Kaplan Maier survival analysis(any failure) revealed that the estimated probability of survival at 1,3,6,12,24, and 34 months of treatment was 91.1%,87.2%,81.2%,75.2%,69.9% and 63.2% respectively. In addition the survival analysis for response failure due to death, the estimated proportion of surviving at 1,3,12,24 and 33 months after treatment were 91.4%,87.5%,82.8%,80.3%,77.9% and 75.3% respectively. The trends demonstrate relatively high decrease in the probability of survival in the first and third months of treatment. This may be related to the high burden of disease and advanced clinical stage of patient at the start of ART. The findings are comparable to the Haitian study that estimated 87% survival probability at 12 months of treatment (80) and the study from Tanzania that estimated 80.8%,71% and 59.3% survival probability at 3,12 and 36 months after treatment respectively(90).The difference could be explained by the social, nutritional or other interventions other than ART.

Determinants of response failure: the analysis using bivariate Cox model reviled that sex being male, age at the start of ART >50years, base line CD4 cell count <100, haemoglobin <10mg/dl, advanced clinical stage (functional status being bedridden and WHO stage 4 and 3), previous exposure to ARV (other than PMTCT), occurrence of side effects during treatment, concurrent intensive phase TB treatment at the start of ART and poor or fair adherence increase the hazards for response failure. However when the variables analyzed using multivariate Cox model only poor or fair adherence, previous exposure to ARV(other than PMTCT),occurrence of side effects, haemoglobin <10mg/dl and functional status bedridden were found to be statistically significant determinants of response failure.

Haemoglobin level as important predictors of disease progression and mortality was also reported in the Tanzanian and other studies (90, 93). Strong association of poor adherence with treatment failure had been also identified in studies from both developed and African countries (89,94,95). The effect of adherence on the treatment outcome is obvious and previous exposure to ARV and its association with response failure may tell about the presence of resistance to ARV. Occurrence of side effects may directly affect the adherence or disrupts the pharmcodynamics or kinetics of ARV, or the presence of drug interaction or poor tolerance of the patient. But it is uncertain whether the association between anaemia and response failure is causal or whether anaemia is rather a marker of progressive HIV diseases. The confounding association between functional status being bedridden and haemoglobin<10mg/dl may give a clue in that anaemia would be a marker of progressive HIV disease.

Limitation

The followings were the limitation of the study and the interpretation and generalization of the findings should be taken cautiously:

First, due to the retrospective and observational design of this study, it was unable to control factors specific to patients (e.g. adverse nutritional and psychosocial issues), facilities infection control measures, programs and diagnostic strictness (e.g. low sensitivity and specificity of x-ray imaging, low sensitivity of AFB).In patients with only one clinic visit we were unable to determine the degree of patient adherence to ART from the patient records. Even though assessing and documentation of patient adherence to ART was standardized it seems it is difficult in the real clinical practice, however, this reflects usual clinical practice and was the strongest predictor for both failure analysis. Lack of information on some risk factor for mortality and the exact cause of mortality and Issues of drug interactions were not available in this study.

Second, possible selection biases of HAART strategy towards patients with more sever disease and also the study was conducted in the hospital setting.

Third, mortality might be underestimated, since patient lost to follow up probably including individuals dying at home without being reported. Although the proportion of patients lost to follow up in this study (9.3%) was comparable to other African studies (90), data quality would be improved with better cohort retention.

Fourth, resistance testing at baseline, and therefore it was difficult to distinguish patients with ART failure because of primary drug resistance from those with ART failure of other causes, including poor adherence. However, primary resistance to ARV drugs is still rare in ARV naïve patients, reports from other African countries strengthens this (89)

Five, although more reliable than the routine clinical follow up data records, National/WHO standard paper formats and registers' data are not as complete and may be less accurate than clinical trial or research data's.

Despite the limitation this study suggests that data collected as part of routine care in standard formats can be used to identify patients at increased risk of failing their ART during their follow up.

Strength

Its Cohort nature, relatively long follow up date used and the first study in the Ethiopian military HIV treatment facilities that evaluates the response to ART and its determinate were the strong side of the study. The use of advanced statistical methods and inclusion of almost all patients who took ART in the facility made the study more strong.

XI. Conclusions

The patterns of response to and failure for ART in Ethiopian military hospital ART clinics are comparable to other resource limited countries, even though mortality were much higher than developed world. Response failure, specially mortality was found to be high, with the majority of death occurs within three months of starting ART. Most of the patients started ART at advanced immunodeficiency stage (both clinical and CD4 count), therefore early diagnosis and treatment of HIV should be well addressed. Adherence problem, previous exposure to ARV, occurrence of side effects and impaired functional status/haemoglobin <10mg/dl are independent predictors of response to and failure for ART. Low base line CD4 count, TB treatment during ART, weight, age and sex are associated in Bivariete analysis with increased hazards for response failure but not significant. There is non significant difference in the response failure for ART in the various regimen of ART. The baseline characteristics' of the patient has important associations with the response to ART. About a quarter of patients had response failure (169, 23.8%) and significant number (66, 9.3%) lost to follow up, even though it was lower than the national reported figures. Statistically non significant using multivariate Cox model, but important association observed was male sex had increased hazard ratio to response failure than female(some studies also describes this(88,91).

XII. Recommendation

For health care workers in the clinical practice:

- In order to avoid late or advanced clinical and immunodeficiency presentation at the start of ART, early diagnosis of HIV patients at various clinics and voluntary testing at the general population should be strengthened. The referral and linkage from HCT service providers and ART clinics should also examined.
- In order to prevent the many deaths that occur during the first three months(especially the first one month) of antiretroviral therapy, health workers should plan for close follow up, identification of risk factors and frequent contact with patients during the early phase of treatment. Patients should also be informed about the need and the importance of close and frequent contacts to avert possible failure of ART.
- Documenting the baseline characteristics of the patient, and clinical stage, body weight, hemoglobin should be viewed as important component of the routine clinical care for patients on antiretroviral therapy.
- Health workers in ART clinics should be prepared to promote, assess possible factors of adherence problem and help their patients adhere to their medication.
- Health care worker should also assess the adherence barriers and the compliance of their patient before dispensing ARV, in order to avert prior exposure to ARV and poor adherence.

For programs managers and decision makers:

- Strategies to identify, diagnose and treat HIV infected patients should be strengthened and the referral and linkages among the various testing centers also should be addressed.

- The need for improving the quality of patient management at early phase of treatment (health care workers capacity, diagnostic capacity for OIs and other infections).
- To practice evidence based medicine, the health care works practice need to be integrated to research practices.
- Strategies to address the barriers of adherence should also be revised and strengthened.
- The high TB occurrence during ART may be due to absence of INH preventive treatment in the health facilities and this should be addressed.
- Clinical documentation practice was encouraging and further work has to be done to reduce some problems and also electronic documentation should be thought.
- Important patients follow up characteristics like BMI(studies identified it as important nutritional status assessment tool and predictors of failure was not be able to calculated since height is not recorded and it should be addressed

For research

- Risk factors or specific determinants of death at the early phase of treatment should be investigated further.
- Factors related to side effects and sex/gender should also be investigated closely.

IX. Reference

1. MOH/FHACO: guidelines for antiretroviral treatment in adolescence and adult in Ethiopia. July 2007.
2. Katherine L Fielding et al. Risk factors for poor virological outcome at 12 months in a workplace-based antiretroviral therapy programme in South Africa: A cohort study. BMC Infectious Diseases 2008, 8:93 doi:10.1186/1471-2334-8-93
3. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA 1999, 282: 2220-6.http://amedeo.com/lit.php?id=1060597
4. Grabar S, Le Moing V, Goujard C, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of HAART. Ann Intern Med 2000, 133: 401-10.
5. Piketty C, Weiss L, Thomas F, et al. Long-term clinical outcome of HIV-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. J Infect Dis 2001, 183:1328-35.
6. Kempf DJ, Rode RA, Xu Y, et al. The duration of viral suppression during protease inhibitor therapy for HIV-1 infection is predicted by plasma HIV-1 RNA at the nadir. AIDS 1998, 12: F9-14.
7. Powderly WG, Saag MS, Chapman S, Yu G, Quart B, Clendeninn NJ. Predictors of optimal virological response to potent antiretroviral therapy. AIDS 1999,13:1873-1880.
8. Raboud JM, Montaner JS, Conway B, et al. Suppression of plasma viral load below 20 copies/ml is required to achieve a long-term response to therapy. AIDS 1998, 12: 1619-24.http://amedeo.com/lit.php?id=9764780
9. Maggiolo F, Migliorino M, Pirali A. Duration of viral suppression in patients on stable therapy for HIV-1infection is predicted by plasma HIV RNA level after 1 month of treatment. J AIDS 2000, 25:36-43.
10. Mezzaroma I, Carlesimo M, Pinter E, et al. Clinical and immunologic response without decrease in virus load in patients with AIDS after 24 months of HAART. Clin Infect Dis 1999, 29:1423-30.
11. Deeks SG. Determinants of virological response to antiretroviral therapy: implications for long-term strategies. Clin Infect Dis 2000, 30 Suppl 2: S177-84.

12. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. Lancet 2004, 364:51-62. http://amedeo.com/lit.php?id=15234856
13. Cozzi-Lepri A, Phillips AN, d'Arminio Monforte A, et al. When to start HAART in chronically HIVinfected patients: evidence from the ICONA study. AIDS 2001; 15:983-90.
14. Phillips AN, Staszewski S, Weber R, et al. HIV viral load response to ART according to the baseline CD4 cell count and viral load. JAMA 2001, 286:2560-7.
15. Le Moing V, Chene G, Carrieri MP, et al. Predictors of virological rebound in HIV-1-infected patients initiating a protease inhibitor-containing regimen. AIDS 2002, 16:21-9.
16. Smith CJ, Sabin CA, Youle MS, et al. Factors influencing increases in CD4 cell counts of HIV-positive persons receiving long-term highly active antiretroviral therapy. J Infect Dis 2004, 190:1860-8.http://amedeo.com/lit.php?id=15499544
17. Smith K, Aga E, Bosch RJ, Valdez H, et al. Long-term changes in circulating CD4 T lymphocytes in virologically suppressed patients after 6 years of highly active antiretroviral therapy. AIDS 2004, 18:1953-6.
18. Viard JP, Burgard M, Hubert JB, et al. Impact of 5 years of maximally successful highly active antiretroviral therapy on CD4 cell count and HIV-1 DNA level. AIDS 2004, 18:45-9.http://amedeo.com/lit.php?id=15090828
19. Valdez H, Connick E, Smith KY, et al. Limited immune restoration after 3 years' suppression of HIV-1 replication in patients with moderately advanced disease. AIDS 2002, 16:1859-66.
20. Kaufmann GR, Furrer H, Ledergerber B, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. Clin Infect Dis 2005;41:361-72. http://amedeo.com/lit.php?id=16007534
21. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch Intern Med 2003; 163:2187-95. http://amedeo.com/lit.php?id=14557216
22. Kaufmann D, Pantaleo G, Sudre P, Telenti A. CD4-cell count in HIV-1-infected individuals remaining viraemic with HAART. Swiss HIV Cohort Study. Lancet 1998, 351:723-4.
23. Deeks SG, Barbour JD, Grant RM, Martin JN. Duration and predictors of CD4 T-cell gains in patients who continue combination therapy despite detectable plasma viremia. AIDS 2002, 16: 201-7.

24. Negredo E, Molto J, Munoz-Moreno JA, et al. Safety and efficacy of once-daily didanosine, tenofovir and nevirapine as a simplification antiretroviral approach. Antivir Ther 2004, 9:335-42.http://amedeo.com/lit.php?id=15259896
25. DeJesus E, McCarty D, Farthing CF, et al. Once-daily versus twice-daily lamivudine, in combination with zidovudine and efavirenz, for the treatment of antiretroviral-naive adults with HIV infection: a randomized equivalence trial. Clin Infect Dis 2004, 39:411-8.
26. Phillips AN, Youle M, Lampe F, et al. CD4 cell count changes in individuals with counts above 500 cells/mm and viral loads below 50 copies/ml on antiretroviral therapy. AIDS 2002; 16: 1073-5.
27. Salzberger B, Rockstroh J, Wieland U, et al. Clinical efficacy of protease inhibitor based antiretroviral combination therapy--a prospective cohort study. Eur J Med Res 1999, 4:449-55.
28. Thiebaut R, Morlat P, Jacqmin-Gadda H, et al. Clinical progression of HIV-1 infection according to the viral response during the first year of antiretroviral treatment. Groupe d'Epidemiologie du SIDA en Aquitaine (GECSA). AIDS 2000, 14:971-8.
29. Reisler RB, Han C, Burman WJ, Tedaldi EM, Neaton JD. Grade 4 events are as important as AIDS events in the era of HAART. J AIDS 2003; 34: 379-86. http://amedeo.com/lit.php?id=14615655
30. Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-98: the EuroSIDA study. Lancet 2000, 356:291-6. http://amedeo.com/lit.php?id=11071184
31. Mocroft A, Brettle R, Kirk O, et al. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. AIDS 2002, 16:1663-71. http://amedeo.com/lit.php?id=12172088
32. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 2003;362:22-9. http://amedeo.com/lit.php?id=12853195
33. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. JAMA 2005, 293:817-29. http://amedeo.com/lit.php?id=1571377
34. Sterne JA, Hernan MA, Ledergerber B, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet 2005, 366:378-84.http://amedeo.com/lit.php?id=16054937

35. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 cell counts of 200 per cubic millimeter or less. ACTG 320 Study Team. N Engl J Med 1997, 337:725-33. http://amedeo.com/lit.php?id=9287227
36. Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. Lancet 1998, 351:543-9. http://amedeo.com/lit.php?id=9492772
37. Stellbrink HJ, Hawkins DA, Clumeck N, et al. Randomised, multicentre phase III study of saquinavir plus zidovudine plus zalcitabine in previously untreated or minimally pretreated HIV-infected patients.Clin Drug Invest 2000, 20:295-307.
38. Arminio Monforte A, Sabin CA, Phillips A, et al. The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy. Arch Intern Med 2005, 165:416-23.
39. Annual Data report from DHD,2008(unpublished)
40. MOH/FHAPCO: Guidelines for implementation of the antiretroviral therapy programme in Ethiopia. July 2007.
41. MOH/DACA/FHACO: guidelines for antiretroviral treatment in adolescence and adult in Ethiopia. January 2005.
42. Mellors JW, Munoz AM, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997, 126:946-954. http://amedeo.com/lit.php?id=9182471
43. Lyles RH, Munoz A, Yamashita TE, et al. Natural history of HIV type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. J Infect Dis 2000, 181:872-880.http://amedeo.com/lit.php?id=10720507
44. Harrington M, Carpenter CC. Hit HIV-1 hard, but only when necessary. Lancet 2000, 355:2147-52.http://amedeo.com/lit.php?id=10902643
45. Lederman MM, McKinnis R, Kelleher D, et al. Cellular restoration in HIV infected persons treated with abacavir and a protease inhibitor: age inversely predicts naive CD4 cell count increase. AIDS 2000, 14:2635-42.
46. Grabar S, Kousignian I, Sobel A, et al. Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. AIDS 2004,18:2029-2038.

47. Phillips AN, Youle M, Lampe F, et al. CD4 cell count changes in individuals with counts above 500 cells/mm and viral loads below 50 copies/ml on antiretroviral therapy. AIDS 2002; 16: 1073-5.
48. Phillips A, CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS 2004,18:51-8.
49. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting HAART: a collaborative analysis of prospective studies. Lancet 2002; 360:119-29. http://amedeo.com/lit.php?id=12126821
50. Phillips AN, Staszewski S, Weber R, et al. HIV viral load response to ART according to the baseline CD4 cell count and viral load. JAMA 2001, 286:2560-7. http://amedeo.com/lit.php?id=11722270
51. Phair JP, Mellors JW, Detels R, et al. Virologic and immunologic values allowing safe deferral of antiretroviral therapy. AIDS 2002; 16:2455-9. http://amedeo.com/lit.php?id=12461420
52. Opravil M, Ledergerber B, Furrer H, et al. Clinical efficacy of early initiation of HAART in patients with asymptomatic HIV infection and CD4 cell count > 350 x 10(6)/l. AIDS 2002, 16:1371-81.http://amedeo.com/lit.php?id=12131214
53. Palella FJ Jr, Deloria-Knoll M, Chmiel JS, et al. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. Ann Intern Med 2003; 138:620-6.http://amedeo.com/lit.php?id=12693883
54. Mocroft A, Phillips AN, Lundgren JD. HIV survival benefit associated with earlier antiviral therapy. Ann Intern Med 2004, 140:578-9. http://amedeo.com/lit.php?id=15068990
55. Casado JL, Perez-Elias MJ, Antela A, et al.Predictors of long-term responses to protease inhibitor therapy in a cohort of HIV-infected patients. AIDS 1998; 12:F131-F135.http://amedeo.com/lit.php?id=9708403
56. Mocroft A, Gill MJ, Davidson W, Phillips AN. Predictors of a viral response and subsequent virological treatment failure in patients with HIV starting a protease inhibitor. AIDS 1998, 12:2161-2167.
57. Mocroft A, Devereux H, Kinloch-de-Loes S, et al. Immunological, virological and clinical response to highly active antiretroviral therapy treatment regimens in a complete clinic population. AIDS 2000,14:1545-1552

58. Miller V, Staszewski S, Sabin C, et al. CD4 lymphocyte count as a predictor of the duration of HAARTinduced suppression of HIV load. J Infect Dis 1999, 180:530-3. http://amedeo.com/lit.php?id=10395876
59. Deeks SG, Hecht FM, Swanson M, et al. HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic: response to both initial and salvage therapy. AIDS 1999, 13:F35-43. http://amedeo.com/lit.php?id=10397555
60. Grabar S, Pradier C, Le Corfec E, et al. Factors associated with clinical and virological failure in patients receiving a triple therapy including a protease inhibitor. AIDS 2000, 14:141-9.http://amedeo.com/lit.php?id=10708284
61. Wood E, Hogg RS, Yip B, et al. Why are baseline HIV RNA levels 100,000 copies/mL or greater associated with mortality after the initiation of antiretroviral therapy? JAIDS 2005;38:289-295.
62. Cozzi Lepri A, Phillips AN, d'Arminio Monforte A, et al. When to start HAART in chronically HIVinfected patients: evidence from the ICONA study. AIDS 2001, 15:983-90. http://amedeo.com/lit.php?id=11399980
63. Le Moing V, Thiebaut R, Chene G, et al. Predictors of long-term increase in CD4(+) cell counts in HIV-infected patients receiving a protease inhibitor-containing antiretroviral regimen. J Infect Dis 2002, 185: 471-80.
64. Holmberg SD, Hamburger ME, Moorman AC, Wood KC, Palella FJ Jr. Factors associated with maintenance of long-term plasma HIV virus RNA suppression. Clin Infect Dis 2003; 37: 702-7.http://amedeo.com/lit.php?id=12942404
65. Wood E, Hogg RS, Yip B, et al. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 x 109 cells/L. Ann Int Med 2003; 139:810-816. http://amedeo.com/lit.php?id=14623618
66. Wood E, Hogg RS, Yip B, et al. The impact of adherence on CD4 cell count responses among HIVinfected patients. J Acquir Immune Defic Syndr 2004, 35:261-8.http://amedeo.com/lit.php?id=15076240
67. Christian Hoffmann: monitoring ART. HIV medicine 2007.www.HIVMedicine.com.com.
68. Garcia F, De Lazzari E, Plana M, et al. Long-Term CD4+ T-Cell Response to Highly Active Antiretroviral Therapy According to Baseline CD4+ T-Cell Count. J AIDS 2004, 36:702-713. http://amedeo.com/lit.php?id=15167289

69. Kaufmann G, Perrin L, Pantaleo G. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: The Swiss HIV Cohort Study. Abstract LB4,9th CROI 2002, Seattle, USA. http://www.retroconference.org//2002/Abstract/14064.htm
70. Piketty C, Castiel P, Belec L, et al. Discrepant responses to triple combination antiretroviral therapy in advanced HIV disease. AIDS 1998, 12:745-50.
71. Renaud M, Katlama C, Mallet A, et al. Determinants of paradoxical CD4 cell reconstitution after protease inhibitor-containing antiretroviral regimen. AIDS 1999, 13:669-76. http://amedeo.com/lit.php?id=10397561
72. Lederman MM. Immune restoration and CD4+ T-cell function with antiretroviral therapies. AIDS 2001,Suppl 2:S11-5. http://amedeo.com/lit.php?id=11424971
73. Lange CG, Valdez H, Medvik K, Asaad R, Lederman MM. CD4+ T-lymphocyte nadir and the effect of highly active antiretroviral therapy on phenotypic and functional immune restoration in HIV-1 infection. Clin Immunol 2002, 102:154-61. http://amedeo.com/lit.php?id=11846457
74. Kaplan JE, Hanson DL, Cohn DL, et al. When to begin HAART? Evidence supporting initiation of therapy at CD4+ lymphocyte counts <350 cells/uL. Clin Infect Dis 2003; 37:951-8. http://amedeo.com/p2.php?id=13130408&s=hiv
75. Sterling TR, Chaisson RE, Moore RD. HIV-1 RNA, CD4 T-lymphocytes, and clinical response to HAART. AIDS 2001, 15:2251-7. http://amedeo.com/p2.php?id=12627368&s=hiv
76. Chene G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. Lancet 2003; 362: 679-686.http://hiv.net/link.php?id=12957089
77. LINDA GORGOS et al: Determinants of Survival for Native American Adults with HIV Infection. AIDS PATIENT CARE and STDs Volume 20, Number 8, 2006
78. ART Cohort Collaboration. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: Analysis of prospective studies. Lancet 2003 Aug 30; 362:679-86.) , Abigail Zuger, M
79. Gregory K. Robbins, et al. Predictors of Antiretroviral Treatment Failure in an Urban HIV Clinic. J Acquir Immune Defic Syndr. 2007 January 1; 44(1): 30–37.
80. Patrice Severe et al: Massachusetts Medical Society Antiretroviral Therapy in a Thousand Patients with AIDS in Haiti N Engl J Med 2005;353:2325-34.

81. Christian Hoffmann and Fiona Mulcahy: when to start HAART. HIV medicine 2007.www.HIVMedicine.com.com.
82. Christian Hoffmann and Fiona Mulcahy: Goals and principles of therapy. HIV medicine 2007.www.HIVMedicine.com.com.
83. Florence E, Lundgren J, Dreezen C, et al. Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. HIV Med 2003;4:255-62. http://amedeo.com/lit.php?id=12859325
84. Viard JP, Mocroft A, Chiesi A, et al. Influence of age on CD4 cell recovery in HIV- infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. J Infect Dis 2001,183: 1290-4. http://amedeo.com/lit.php?id=11262215
85. Jerene et al; 2006 licensee BioMed Central Ltd: Antiretroviral therapy at a district hospital in Ethiopia prevents death and tuberculosis in a cohort of HIV patients. AIDS Research and Therapy 2006, 3:10 doi: 10.1186/1742-6405-3-10.
86. Degu Jerene Dare: HIV antiretroviral therapy in Ethiopia,2007 Available at http://www.etharc.org/
87. Mesert Molla: ART services quality in Ethiopian military hospital - thesis final.2008
88. Lawn et al: CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in Sub-Saharan Africa. BMC infectious Disease 2006, 6:59 doi: 10.1186/1471-2334-6-59.
89. Messou et al: anthropometric and immunological success of antiretroviral therapy and prediction of virological success in West African adults. Bull World Health Organ.2008 June;86(6):435 – 442
90. Johannessen et al: Predictors of mortality in HIV – infected patients starting antiretroviral therapy in a rural hospital in Tanzania. BMC infectious Disease 2008,8:52 doi:10.1186/1471-2334-8-52
91. Hogg RS et al: Rates of disease progression by baseline CD4 cell count and viral load after initiating triple – drug therapy.PMID:11722271/JAMA
92. Importance of baseline prognostic factors with increasing time since initiation of HAART: Collaborative analysis of cohorts of HIV -1-infected patients.J Acquir Immune Defic Sundr.2007 Dec 15:46(5):607 -15
93. Langford et al; Predictors of disease progression in HIV infection: a review. AIDS Research and Therapy 2007, 4:11 doi:10.1186/1742-6405-4-11

94. Gregory K. Robbins, et al. Predictors of Antiretroviral Treatment Failure in an Urban HIV Clinic. J Acquir Immune Defic Syndr. 2007 January 1; 44(1): 30–37.
95. Wood et al: Impact of baseline viral load and adherence on survival of HIV – infected adults with baseline CD4 cell counts>=200 cells/Ml. AIDS 2006, 20:1117-1123.
96. Dragsted UB, Mocroft A, Vella S, et al. predictors of immunological failure after initial response to highly active antiretroviral therapy in HIV-1-infected adults: A EuroSIDA study. J Infect Dis 2004,190:148-55.
97. Teixeira L, Valdez H, McCune JM, et al. Poor CD4 T cell restoration after suppression of HIV-1 replication may reflect lower thymic function. AIDS 2001, 15:1749-56.http://amedeo.com/lit.php?id=11579235
98. Paton NI et al: The impact of malnutrition on survival and the CD4 count response in HIV – infected patients starting antiretroviral therapy. PMID: 16945078/InterScience.